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Dated 13 January 2005

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The Patent Office

Cardiff Road, Newport
South Wales NP9 1RH

1. Your reference — JDMA/RMW/P203269

18 MAR 2004

2. Patent application num *(The Patent Office will fill i* — 0406137.0

19MAR04 E882156-1 D02835
P01/7700 0.00-0406137.0 NONE

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

PFIZER LIMITED
RAMSGATE ROAD
SANDWICH
KENT CT 13 9NJ

Patents ADP number *(if you know it)* 06892673001

If the applicant is a corporate body, give the country/state of its incorporation — GB

4. Title of the invention — SUBSTITUTED PYRAZOLES

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

URQUHART-DYKES & LORD
TOWER HOUSE
MERRION WAY
LEEDS
LS2 8PA

Patents ADP number *(if you know it)* 1644004

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day/month/year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day/month/year)*

8. Is a statement of inventorship and or right to grant of a patent required in support of this request? *(Answer "Yes" if:)*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
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YES

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Continuation sheets of this form	
Description	157
Claim(s)	0
Abstract	0
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Priority documents	0
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Statement of inventorship and right to grant of a patent *(patents form 7/77)*	0
Request for preliminary examination and search *(patents form 9/77)*	0
Request for substantive examination *(patents form 10/77)*	0
Any other documents *(please specify)*	0

11 I/We request the grant of a patent on the basis of this application
Signature Date 18/03/04

URQUHART-DYKES & LORD

12 Name and daytime telephone number of person to contact in the United Kingdom

JONATHAN D M ATKINSON
0113 245 2388

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Substituted Pyrazoles

The present invention relates to pesticidal compounds and a process for their preparation. More particularly, the present invention relates to *N*-(1-arylpyrazol-4-yl)sulfonamides which possess antiparasitic activity. In particular, we have identified a series of *N*-(1-arylpyrazol-4-yl)sulfonamides which have improved activity and / or a longer duration of action and / or improved safety.

Arylpyrazoles are described widely in the prior art for a number of uses as discussed below.

Certain pyrazole derivatives possessing, *inter alia*, antiparasitic activity are already known. European Patent Publication Nos EP-0295117, EP-0234119, EP-0946515, EP-0871617, EP-0846686 and EP-0918756 describe many arylpyrazoles which are used as antiparasitics.

For example, EP-A-0234119 discloses 1-arylpyrazoles for the control of arthropod, plant nematode and helminth pests. 1-arylpyrazoles are also disclosed in EP-A-0295117; in addition to having arthropodicidal, plant nematocidal and antihelminthic activity, these compounds are reported to display antiprotozoal properties. Similar profiles of activity are also displayed by the 1-arylpyrazoles disclosed in EP-A-0295118.

EP-A-0280991 discloses further 1-arylpyrazoles having insecticidal activity, WO-A-97/07102 describes other 1-arylpyrazoles with parasiticidal properties and EP-A-0780378 relates to 1-arylpyrazoles and 1-heteroarylpyrazoles and their use as pesticides.

WO-9824767, EP-933363, and EP-957094 describe 4-cyclopropylarylpyrazoles having parasiticidal activity for the control of arthropods.

EP-963695 and US-6313157 disclose the use of 1-arylpyrazoles for the control of fleas on cats and dogs.

WO-0224656 discloses 4-amidopyrazoles which are stated to have bacteriocidal, fungicidal, insecticidal and nematocidal activity and which have agricultural or horticultural use.

Sulphamoyl (reversed sulphonamides) arylpyrazoles for the control of arthropod, plant nematode, or helminth pests have also been disclosed in, for example, EP-234119, US-2002016333, WO-0258690, DE-19511269.

5-sulphonamido-1-arylpyrazoles have been disclosed as having utility as herbicides in, for example, EP-0192951 and EP-302328.

US-5618945 relates to a process for sulphinylation of compounds such as arylpyrazoles, by the treatment of a compound such as RS(O)X, where X is commonly Cl, and discloses compounds of formula R-S(O)NH-Het where Het can be *N*-arylpyrazole, although it is not clear which substitution pattern is referred to.

Some pyrazoles possessing bactericidal activity are disclosed in WO-9315060 foruse in crop protection. Among the many structures disclosed are some *N*-heterocyclic pyrazol-4-yl sulfonamides.

In WO-9315060 the compounds are only used as phytopathogenic microbicides (bacterial parasites on a plant host) and not for the control or treatment of arthropods. Since, the compounds of this patent are intended for a different use it is speculated that different structural considerations for ensuring efficacy apply.

The prior art compounds do not always demonstrate good activity or a long duration of action against parasites. Similarly, some parasiticidal agents are useful only for a narrow spectrum of parasites. Modern pesticides must meet many demands, including long duration, broad spectrum of action, low toxicity, combination with other active substances and/or different formulation excipients. The occurrence of resistance is also possible. Consequently the search for new antiparasitic agents is ongoing and there is a constant demand for novel compounds which are advantageous over the known compounds in one or more of these aspects.

The aim of the present invention is to provide a compound which can be conveniently administered as an antiparasitic agent. In particular an agent is sought which can be used in the treatment of human or animal parasitic diseases or can be used in agricultural or horticultural applications. One aim is to provide an agent which can be used in humans, livestock (including sheep, pigs and cattle), companion animals (including cats, dogs and horses). The agent is intended to control arthropods, arachnids, nematodes and helminths including flies, fleas, mites and ticks.

Another aim is to provide compounds with good pharmacokinetics and extended duration of action and thus which prevents re-establishment of infestation over long periods of time.

It is a further aim to provide a compound suitable for oral, parenteral or topical administration which is able to kill existing parasites and prevent infestation. This has benefits in terms of compliance and labour costs as less frequent dosing is needed and the dosing timetable is easier. This in turn assists in minimising the re-incidence of infestation as a subsequent dosage is less likely to be overlooked.

It is an aim of the present invention to overcome various disadvantages of or improve on the properties of prior art compounds. Thus it is an aim of the invention to provide an arylpyrazole which has improved activity relative to prior art compounds against parasites. The compounds of the present invention have especially good ability to control a broad spectrum of arthropods as shown by the results of tests demonstrating their potency and efficacy. Surprisingly, we have found that the compounds of the present invention are significantly more active against fleas and / or have a greater duration of action than similar prior art compounds. One advantage of the compounds of the present invention is that treatment with these compounds can also lead to a reduced incidence of allergy to the parasite which is responsible for the infestation. For example, the incidence of flea allergies which can cause flea allergic dermatitis may be reduced.

It is also desirable that the compounds of the present invention should have an improved pharmacokinetic profile, improved safety, longer half life, improved

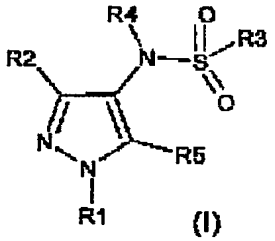
persistence and improved solubility. It is also desired that the compounds should lead to a reduced incidence of emesis.

Unfortunately, many potent pesticidal aryl pyrazoles and their derivatives also have undesirable effects such as emesis on animals regardless of whether or not the animal itself is being treated directly. This unwanted toxicity can limit the dose that can be used and thus limits the range of parasites that can be controlled. Thus it is an aim of the present invention to address the need for the development and use of new and efficacious pesticides that can control pests for longer periods of time but which are not toxic to animals susceptible to pest infestations or animals that might come into contact with areas susceptible to pest infestations.

It is a further aim to provide a convenient, synthetically efficient process for the production of the aryl pyrazoles and the intermediates of the present invention. It is also an aim to provide a route to the compounds of the invention which offers a good yield and which ideally avoids the use of unnecessary synthetic steps and /or purification steps.

The present invention satisfies some or all of the above aims.

According to the present invention, there is provided a compound of formula (I) or a pharmaceutically, veterinarily or agriculturally acceptable salt or solvate thereof:



(I)

wherein

R^1 is aryl or heteroaryl optionally substituted by one or more groups independently selected from: hydrogen; halo; C_{1-6} alkyl; C_{1-6} alkoxy which may be optionally substituted with one or more independently selected halo atoms; $-S(O)_nC_{1-6}$ alkyl; and pentafluorothio; cyano; C_{1-6} alkanoyl which may be optionally substituted with one or more independently selected halo atoms;

R^2 is selected from: hydrogen; halo; C_{1-6} alkyl; $-S(O)_nC_{1-6}$ alkyl; $-(CH_2)_m$ C_{3-6} cycloalkyl which may be optionally substituted with one or more substituents independently selected from: halo and C_{1-6} alkyl; cyano; nitro; $-(CH_2)_m$ NR^aR^b; C_{1-6} alkanoyl which may be optionally substituted by one or more groups independently selected from halo and C_{1-4} alkoxy; phenyl; oxadiazole; $-C(O)NR^aR^b$; $-NR^aC(O)R^b$; C_{2-6} alkenyl; and C_{2-6} alkynyl;

R^3 is selected from: C_{1-6} alkyl; $-(CH_2)_m$ NR^aR^b; $-(CH_2)_m$ C_{3-6} cycloalkyl which may be optionally substituted with one or more substituents independently selected from: halo and C_{1-6} alkyl; $-(CH_2)_m$ phenyl; -CH=CH-phenyl; and $-(CH_2)_m$ het;

R^4 is selected from: hydrogen; C_{1-6} alkyl; $-(CH_2)_m$ C_{3-6} cycloalkyl which may be optionally substituted with one or more substituents independently selected from: halo and C_{1-6} alkyl; $-(CH_2)_m$ $S(O)_pR^6$; $-CO_2(C_{1-6}$ alkyl); $-(CH_2)_m$ het; and $-C(O)NR^aR^b$;

or R^3 and R^4 taken together with the nitrogen and sulphur atoms to which they are attached form a 4 to 7-membered ring;

R^5 is selected from: hydrogen; hydroxy; C_{1-6} alkyl; NR^aR^b; halo and C_{1-6} alkoxy;

R^6 is selected from: C_{1-6} alkyl; NR^aR^b; C_{3-6} cycloalkyl which may be optionally substituted with one or more substituents independently selected from: halo and C_{1-6} alkyl; het; and phenyl;

each n is independently 0, 1 or 2;

each m is independently 0, 1, 2 or 3;

p is 1or 2;

and wherein

het represents a four- to seven-membered heterocyclic group, which is aromatic or non-aromatic and which contains one or more heteroatoms selected from nitrogen, oxygen, sulfur and mixtures thereof, and wherein said heterocyclic ring is optionally substituted and/or terminated where the valence allows with one or more substituents selected from: halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, OC(O) C_{1-6} alkyl, C(O)C_{1-6} alkyl, C(O)OC_{1-6} alkyl , and NR^aR^b;

each C_{1-6} alkyl group can independently be branched or unbranched and optionally substituted by one or more groups selected independently from: cyano; halo; hydroxy; nitro; C_{1-6} alkoxy; NR^aR^b; $S(O)_n$ C_{1-6} alkyl; $S(O)_n$ C_{3-8} cycloalkyl; $S(O)_n$ C_{1-6} alkylhet; C_{3-8} cycloalkyl; and phenyl;

each phenyl may be optionally substituted by one or more substituents independently selected from: cyano; halo; hydroxy; nitro; C_{1-6} alkyl; C_{1-6} haloalkyl; and C_{1-6} alkoxy; and

each R^a and R^b are independently selected from hydrogen; C_{1-6} alkyl; and C_{3-8} cycloalkyl which may be optionally substituted with one or more substituents independently selected from: halo and C_{1-6} alkyl; or R^a and R^b may be taken together with the nitrogen atom to which they are attached to form a 4 to 7-membered ring.

In an embodiment, it is preferred that R^1 is phenyl or pyridyl, and it is more preferred that R^1 is phenyl.

Preferably, the R^1 group when it is phenyl is tri-substituted, and more preferably it is substituted at the 2-, 4-, and 6- positions with an optional substituent selected from the group comprising: halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, SF_5 and -$COOC_{1-8}$ alkyl, wherein each of these optional substituent groups may itself be

substituted where chemically possible by one or more halogen atoms selected independently.

More preferably, R^1 is 2,4,6-trisubstituted phenyl wherein the 2- and 6-substituents are each independently selected from: hydrogen and halo; and the 4-substituent is selected from: C_{1-4} alkyl which may be optionally substituted with one or more independently selected halo atoms, C_{1-4} alkoxy which may be optionally substituted with one or more independently selected halo atoms; $S(O)_nC_{1-4}$ alkyl which may be optionally substituted with one or more independently selected halo atoms; halo and pentafluorothio;

More preferably, R^1 is a phenyl group which bears substituents at the 2-, 4-, and 6-positions, the substituents at those positions being independently selected from chloro, trifluoromethyl, trifluoromethoxy, and pentafluorothio.

Still more preferably, R^1 is a phenyl group in which the 2- and 6- substituents are chloro and the 4- substituent is selected from: trifluoromethyl, trifluoromethoxy, and pentafluorothio.

It is also preferred that R^1 is 3,5-disubstituted pyridin-2-yl wherein the 3-substituent is selected from: hydrogen and halo; and the 5-substituent is selected from: C_{1-6} alkyl optionally substituted as defined above; C_{1-6} alkoxy which may be optionally substituted with one or more independently selected halo atoms; $S(O)_nC_{1-6}$ alkyl; halo and pentafluorothio.

Preferably het represents a 5- or 6-membered heterocyclic group containing 1, 2 or 3 heteroatoms, which are independently selected from 1 N atom, 1 or 2 O atoms and 1 or 2 S atoms.

More preferably, het is preferably selected from pyrazolyl, imidazolylyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furanyl, thiophenyl, pyrrolyl, and pyridyl wherein the aforementioned groups may be optionally substituted by one or more groups independently selected from C_{1-6} alkyl and halogen.

More preferably, het is selected from: pyridyl, pyrazolyl, oxazolyl and isoxazolyl.

Most preferably, het is selected from: pyridyl and oxazolyl.

Preferably, R^2 is selected from C_{1-6} alkyl; and C_{3-8} cycloalkyl which may be optionally substituted with one or more substituents independently selected from: halo and C_{1-6} alkyl; C_{1-6} alkanoyl which may be optionally substituted by one or more groups independently selected from halo and C_{1-4} alkoxy; cyano; and halo.

More preferably R^2 is selected from C_{1-6} alkyl; and cyano.

Still more preferably R^2 is selected from trifluoromethyl and cyano.

Most preferably R^2 is cyano.

Preferably, R^3 is selected from: C_{1-6} alkyl; NR^aR^b where R^a and R^b are as defined above; $-(CH_2)_m$ C_{3-8} cycloalkyl; $-(CH_2)_m$ phenyl; and -CH=CH-phenyl.

More preferably, R^3 is selected from: C_{1-6} alkyl, C_{3-8} cycloalkyl and $-(CH_2)_m$ phenyl.

More preferably R^3 is selected from: methyl, trifluoromethyl, ethyl, 2,2,2-trifluoroethyl, propyl, isopropyl, cyclopropyl, cyclohexyl, phenyl optionally substituted by halo, and benzyl.

Most preferably R^3 is selected from: methyl, trifluoromethyl, ethyl, 2,2,2-trifluoroethyl, and cyclopropyl.

Preferably, R^4 is selected from: hydrogen: C_{1-6} alkyl; $-(CH_2)_m$ C_{3-8} cycloalkyl; $-(CH_2)_m S(O)_pR^6$ where R^6 is selected from: C_{1-6} alkyl, C_{3-8} cycloalkyl which may be optionally substituted with one or more substituents independently selected from: halo and C_{1-6} alkyl, and $-(CH_2)_m$ phenyl; $-(CH_2)_mS(O)_nC_{3-8}$ cycloalkyl; $-(CH_2)_m S(O)_n$ phenyl; $-(CH_2)_m S(O)_nNR^aR^b$; and $-(CH_2)_m$ phenyl.

More preferably, R^4 is selected from: hydrogen, methyl, ethyl, isopropyl, cyclopropylmethyl, cyanomethyl, pyridin-2-ylmethyl, benzyl, 2,2,2-trifluoroethyl, (1-methylcyclopropyl)methyl, methylcarbamate, 1,1,1-trifluoromethanesulfonyl, (5-methylisoxazoly-3-yl)methyl, cyclobutyl, cyclopentyl, dimethylaminosulfonyl, methylsulfonyl, (methylsulfonyl)methyl, 2-hydroxyethyl, 1-(trifluoromethyl)cyclopropylmethyl, 4-fluorobenzenesulfonyl, 2,4-difluorobenzenesulfonyl, 2,2,2-trifluoroethyl, 2,2,2-trifluoroethanesulfonyl, 1-(trifluoromethyl)cyclopropylmethyl, and 2,2-difluorocyclopropyl.

Most preferably, R^4 is selected from: hydrogen, methyl, 2,2,2-trifluoroethyl, methylsulfonyl, and 1-(trifluoromethyl)cyclopropylmethyl.

Preferably, R^5 is $-(CH_2)_m NR^aR^b$ where R^a and R^b are as defined above, more preferably where m=0, and most preferably R^5 is amino.

Preferably, R^6 is selected from: hydrogen, C_{1-6} alkyl; C_{3-8} cycloalkyl; and phenyl.

Most preferably R^6 is selected from: methyl, trifluoromethyl, ethyl, 2,2,2-trifluoroethyl, and cyclopropyl.

Thus, a preferred group of compounds of formula (I) of the present invention are those wherein:

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-3,4-difluorobenzenesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}cyclopropanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*,*N*-dimethylsulfamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-1-phenylmethanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-2,2,2-trifluoroethanesulfonamide

(*E*)-*N*-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-2-phenylethylenesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}propane-1-sulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-methylpropane-1-sulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(2-hydroxyethyl)methanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}propane-2-sulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-[(methylsulfonyl)methyl]methanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(cyclopropylmethyl)-*N'*,*N'*-dimethylsulfamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(cyclobutylmethyl)methanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(methylsulfonyl)cyclopropanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(cyclopropylmethyl)methanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(cyanomethyl)methanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(pyridin-2-ylmethyl)methanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-benzylmethanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-methylethanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-methylcyclopropanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-methyl-2,2,2-trifluoroethanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-1-(methylsulfonyl)ethanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-ethylmethanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-isopropylmethanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*,*N'*,*N'*-trimethylsulfamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(2,2,2-trifluoroethyl)methanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-[(1-methylcyclopropyl)methyl]methanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(cyclopropylmethyl)-1,1,1-trifluoromethanesulfonamide

Methyl 5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl(methylsulfonyl)carbamate

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(methylsulfonyl)-1,1,1-trifluoromethanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-[(5-methylisoxazol-3-yl)methyl]methanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-cyclobutylmethanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-{[1-(trifluoromethyl)cyclopropyl]methyl}methanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-cyclopentylmethanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-[(dimethylamino)sulfonyl]methanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(methylsulfonyl)-2,2,2-trifluoroethanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-{[1-(trifluoromethyl)cyclopropyl]methyl}-1,1,1-trifluoromethanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(methylsulfonyl)-4-fluorobenzenesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(methylsulfonyl)-2,4-difluorobenzenesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-isopropyl-1,1,1-trifluoromethanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-cyclopentyl-1,1,1-trifluoromethanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1*H*-pyrazol-4-yl}-*N*-(methylsulfonyl)methanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1*H*-pyrazol-4-yl}-*N*-methyl-1,1,1-trifluoromethanesulfonamide

N-{3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-methyl-1,1,1-trifluoromethanesulfonamide

N-{3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1*H*-pyrazol-4-yl}-*N*-(methylsulfonyl)methanesulfonamide

N-{3-cyano-1-[2,6-dichloro-4-trifluoromethylphenyl]-1*H*-pyrazol-4-yl}-*N*-(methylsulfonyl)methanesulfonamide

N-{3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}methanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-cyclobutyl-1,1,1-trifluoromethanesulfonamide

N-{3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(2,2,2-trifluoroethyl)methanesulfonamide

N-{3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-[(5-methylisoxazol-3-yl)methyl]methanesulfonamide

N-{3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-2,2,2-trifluoroethanesulfonamide

N-{3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(methylsulfonyl)-2,2,2-trifluoroethanesulfonamide

N-{3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-{[1-(trifluoromethyl)cyclopropyl]methyl}methanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1*H*-pyrazol-4-yl}-*N*-(methylsulfonyl)-2,2,2-trifluoroethanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1*H*-pyrazol-4-yl}-*N*-(2,2,2-trifluoroethyl)methanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1*H*-pyrazol-4-yl}methanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1*H*-pyrazol-4-yl}-*N*-{[1-(trifluoromethyl)cyclopropyl]methyl}methanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(2,2-difluorocyclopropyl)methanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-trifluoromethylphenyl]-1*H*-pyrazol-4-yl}-*N*-(methylsulfonyl)methanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}methanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-methylmethanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-methyl-1,1,1-trifluoromethanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}ethanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-[(methylthio)methyl]methanesulfonamide

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-1-(methylsulfonyl)methanesulfonamide

Compounds of formula (I) possess parasiticidal activity in humans animals and agriculture. They are particularly useful in the control of ectoparasites.

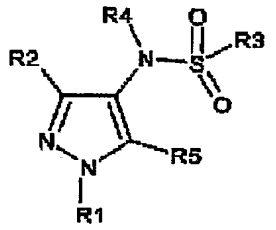
In a further aspect, the present invention provides a process for the preparation of a compound of formula (I), or a pharmaceutically, veterinarily or agriculturally acceptable salt thereof, or a pharmaceutically, veterinarily, or agriculturally acceptable solvate (including hydrate) of either entity, as illustrated below.

The following processes are illustrative of the general synthetic procedures which may be adopted in order to obtain the compounds of the invention.

When one or more of R^1, R^2 and R^5 contain reactive functional groups then additional protection may be provided according to standard procedures during the synthesis of compounds of formula (I). For the synthetic precursors of the compounds of formula (I) the definitions of the groups R^1, R^2 and R^5 therefore necessarily include suitably protected variants P^1, P^2 and P^5 of the defined functional groups as required in each of the intermediate compounds. Other suitable protecting groups for these functionalities are described in the references listed below and the use of these protecting groups where needed is specifically intended to fall within the scope of the processes described in the present invention for producing compounds of formula (I) and its precursors.

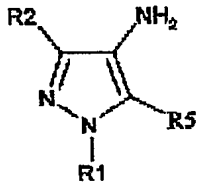
An illustrative example is when R^5 in formula (I) is an unsubstituted amino group, certain precursors may require protection in order to perform the necessary transformations, here P^5 amongst others may include a formamidine group.

A compound of formula (I)



(I)

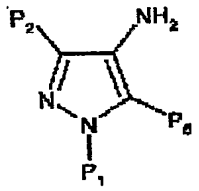
in which R^4 is SO_2R^6 and wherein R^1, R^2, R^3, R^5 and R^6 are as previously defined for formula (I) may be prepared by sulphonation of the amine (II):



(II)

wherein R^1, R^2 and R^5 are as previously defined for formula (I). The sulfonation process used will depend on whether R^3 and R^4 are the same or different.

When the compound of formula (II) contains reactive functionality which is incompatible with the sulfonation of the amine group at the 4-position the compound of formula (II) may be converted to a compound of formula (III) before sulfonation

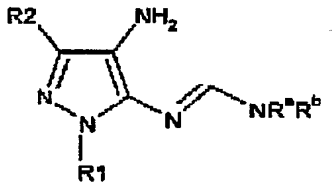


(III)

in which one or more of R^1, R^2 and R^5 have been protected as groups P^1, P^2 and P^5 as necessary as described in the references listed below.

For example, we have found that when R^5 in the compound of formula (II), or any of the other intermediates, is an unsubstituted amino group (which may be also reactive in the sulphonation reaction and thus lead to an unwanted product) a good protecting group for protecting this functionality is a formamidine group.

Thus, conversion of such compound of formula (II) to a compound of formula (IIIA)

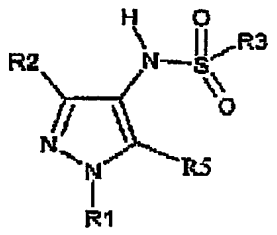


(IIIA)

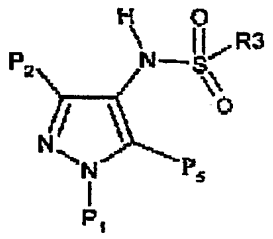
wherein R^1, R^2, R^a, and R^b are as defined for formula (I), or in which R^1 and R^2 are suitably protected as groups P^1 and P^2 as necessary, by reaction with the corresponding N,N dialkylformamide-dimethylacetal is of particular utility in an initial step in the preparation of a compound of formula (I) from a compound of formula (II).

When R^3 is the same as R^5, bis-sulphonation can be achieved by addition of the sulphonyl chloride, R^3SO_2Cl, to a solution of (II) or, to the suitably protected derivative (III) of the compound of formula (II) in a suitable solvent in the presence of base at 0°C. The reaction mixture is then allowed to warm to room temperature and allowed to stand, typically for periods of 2 – 18 hours. Typical reaction conditions use dichloromethane as solvent with triethylamine as base or pyridine as both solvent and base.

When R^3 is not the same as R^5, compounds of formula (I) may be prepared by a two step sulphonation procedure via the monosulfonated compound of formula (IV) or (IVA):



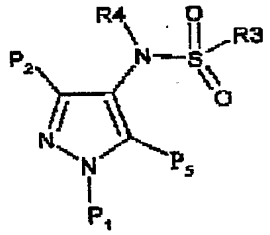
(IV)



(IVA)

wherein R^1, R^2, R^3 and R^5 are as previously defined for formula (I) and groups P^1, P^2 and P^5 are suitable protecting groups by the addition of a sulphonyl chloride, R^3SO_2Cl, to a solution of compound (II) or (III) in a suitable solvent, for example, dichloromethane, in the presence of base, typically pyridine/4-dimethylaminopyridine mixtures, under an inert atmosphere to produce a compound of formula (IV) or (IVA), respectively. The reaction is allowed to stand at room temperature for several hours, typically overnight.

Compounds of formula (IV) or (IVA) may be further sulphonated, for example, by the addition of a sulphonyl chloride, R^6SO_2Cl, to a solution of compound (IV) or (IVA) in a suitable solvent, typically dichloromethane, in the presence of base, for example, triethylamine or pyridine/4-dimethylaminopyridine mixtures to give a compound of formula (I) or a compound of formula (IA):



(IA)

respectively, wherein R^3 and R^4 are as defined in formula (I) and P^1, P^2, and P^5 are suitable protecting groups.

The reaction is allowed to stand at room temperature for several hours, typically overnight.

When P^5 is a protected amine group, for example a formamidine group, deprotection after sulfonation to yield compounds of formula (I) is facilitated using standard conditions described in the literature. Thus, when protection constitutes a formamidine group, refluxing for 4 - 100 hours in a solvent such as methanol, dioxane or tetrahydrofuran with an acid such as hydrochloric acid liberates the amino functionality. Deprotection of formamidines may also be facilitated by

heating in aqueous methanol (typically 1:1 mixtures) with an acid such as hydrochloric acid, at temperatures ranging from 80 – 95°C for 4 – 170 hours.

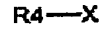
In an alternative process when R^3 is not the same as R^6, compounds of formula (I) or (IA) may be prepared in a one-pot procedure by sequential addition of sulphonyl chlorides, R^3SO_2Cl and R^6SO_2Cl to a solution of compound (II) or (III), respectively, in a suitable solvent, for example dichloromethane, in the presence of base, such as pyridine. The interval between additions is several hours, typically 2 hours, and the reaction is allowed to stand at room temperature for an extra period of several hours, typically overnight. When P^5 in the compound of formula (IA) is a protected amine, deprotection to yield compounds of formula (II) is facilitated as described above using standard conditions.

Compounds of formula (IV) or (IVA) may also be prepared by base catalysed mono-desulphonation of compounds of formula (I) or (IA) in which R^4 is SO_2R^6. Such methods include stirring (I) or (IA) with sodium hydroxide in trifluoroethanol in an inert atmosphere for several hours or stirring with potassium carbonate in methanol/tetrahydrofuran mixtures for several hours.

Compounds of formula (I) may also be prepared by addition of a sulphonyl chloride, R^6SO_2Cl, to a solution of (IV) or (IVA) in a suitable solvent, for example dichloromethane, in the presence of base, such as triethylamine or pyridine/4-dimethylaminopyridine mixtures. The reaction is allowed to stand at room temperature for several hours, typically overnight, yielding compounds of formula (I) or (IA), respectively.

Alternatively, sulphonation of (IV) or (IVA) can be achieved by addition of a sulphonic acid anhydride to a solution of compound (IV) or (IVA) in a suitable solvent, for example dichloromethane, in the presence of base, such as triethylamine, at 0°C. The reaction is allowed to warm to room temperature and allowed to stand for several hours, yielding compounds of formula (I) or (IA), respectively.

A compound of formula (I) or (IA) in which R^4 is C_{1-6} alkyl may be prepared by alkylation of a compound (IV) or (IVA). Alkylation is achieved by reaction of the compound of formula (IV) or (IVA) with an alkylating agent (V):



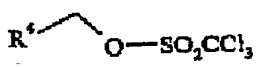
(V)

wherein X may be any leaving group, typically I, Br, Cl, OTs, OTf, O-mesylate, or O-trichloromethylsulphonate, in a suitable solvent in the presence of base.

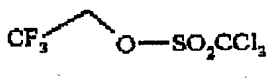
Various solvents may be used for the alkylation reaction including acetone, dichloromethane, acetonitrile, dimethylformamide and N-methylpyrrolidinone. A variety of bases may also be used including potassium carbonate, caesium carbonate, and sodium hydride. Other salts may aid the reaction, for example, sodium iodide may optionally be used with potassium carbonate and potassium iodide may optionally be used with caesium carbonate. Reactions may be carried out over a range of temperatures from 15° – 80°C for times ranging from 1 – 170 hours and may be performed in an inert atmosphere.

More specifically, when R^4 is methyl, then alkylation is achieved by stirring an acetone solution of (IV) or (IVA), methyl iodide and potassium carbonate at room temperature for several hours, typically 18 hours.

Sometimes stronger reaction conditions are required, for example, where R^4 is a haloalkyl group such as CF_3CH_2-, and the compound of formula (I) or (IA) may be prepared from (IV) or (IVA), using a halogenated sulfonate (VI) such as the trichloromethylsulfonate (VIA), and sodium hydride in N-methylpyrrolidinone at elevated temperature, typically 65°C, for 18 hours.



(VI)

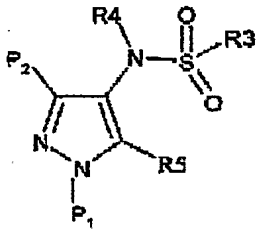


(VIA)

In some instances the alkylating agent may be prepared *in situ*, for example the mesylate from 1-methylcyclopropanemethanol may be prepared by a reaction with methanesulphonyl chloride in dichloromethane using triethylamine/4-dimethylaminopyridine as base. After stirring at room temperature for several hours, the reaction mixture is concentrated *in vacuo* and used for the alkylation of (VI) or (VIA) using potassium carbonate and potassium iodide in dimethylformamide at 80°C.

A compound of formula (I) or (IA) in which R^4 is $CO_2(C_{1-6}$ alkyl) may be prepared by acylation of (IV) or (IVA), respectively. Acylation of (IV) or (IVA) may be effected by reaction with a chloroformate. The reaction is carried out in a suitable solvent, such as acetone at reflux temperature for several hours, typically 3 hours, using potassium carbonate as a base.

A compound of formula (I) or (IB) in which R^5 is H, may be prepared by the diazotisation of a compound of formula (I) or (IB) in which R^5 is NH_2. A variety of diazotisation procedures may be used.



(IB)

Particularly useful is the dropwise addition of *tert*-butyl nitrite to a solution of the amine in tetrahydrofuran at room temperature. The reaction mixture is then heated at reflux for several hours, typically overnight, to give the compound of formula (I) or (IB) in which R^5 is H.

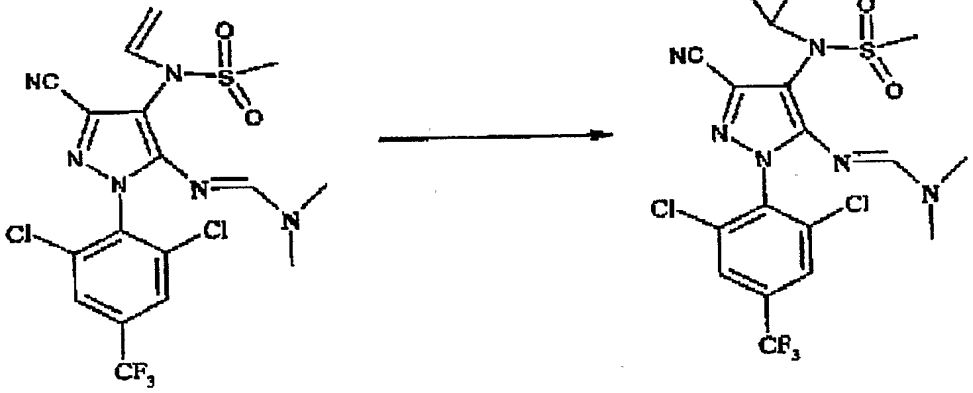
Standard chemical procedures may be used to modify sidechain R^4 of compounds of formula (I) provided that any reactive functional groups in R^1, R^2, R^3 and R^5 are appropriately protected. Thus suitably protected variants P^1, P^2, P^3 and P^5 of those functional groups are described in the references listed below and the use of these protecting groups, where needed, is specifically intended to fall within the

scope of the processes described in the present invention for producing compounds of formula (I).

For example, when R^4 is $BrCH_2CH_2$- then standard dehydrobromination procedures will produce the N-ethenyl derivative. Specifically, such compounds can be dehydrobrominated to give the corresponding N-ethenyl derivative by stirring a solution of the brominated starting material with 1,8-diazabicyclo[5,4,0]undec-7-ene in dimethyl sulphoxide at room temperature for several hours, typically overnight.

Additionally, compounds of formula (I) wherein R^4 is alkenyl, such as ethenyl, will undergo standard cyclopropanation procedures to produce the corresponding cyclopropanated derivative.

For example, a solution of the ethenyl derivative (1) can be converted to the difluorocyclopropyl derivative (2). The compound (1), methyl benzoate and sodium fluoride in toluene are heated to 100°C. Trimethylsilyl-2,2-difluoro-2-(fluorosulphonyl)acetate is added dropwise over several hours, typically 2 hours, to give (2).

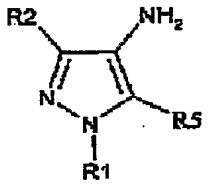


(1) (2)

When R^4 can be readily oxidised, then such groups may transformed using conventional oxidation procedures. For example, sulphides may be readily

oxidised to sulphones using standard oxidising agents, such as those described in "Handbook of Reagents for Organic Synthesis – Oxidising and Reducing Agents" edited by S.D.Burke and R.L.Danheiser. A typical reaction uses Oxone and sodium carbonate in aqueous acetone at room temperature, stirring for several hours, typically 5 hours.

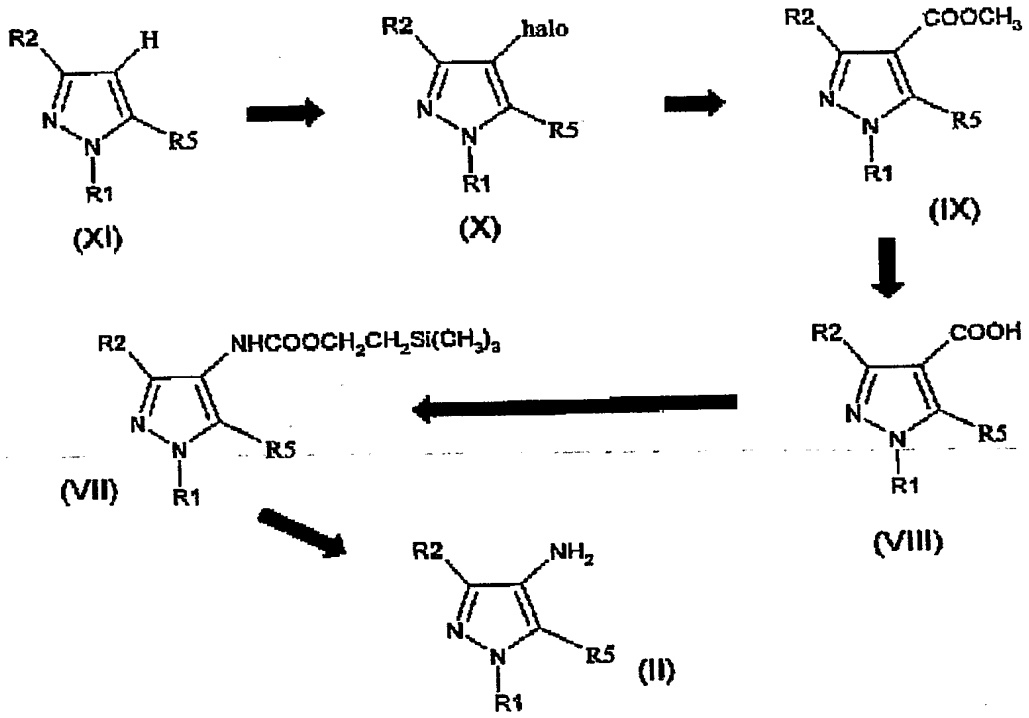
A compound of formula (II) is a key intermediate for the preparation of (I).



(II)

wherein R^1, R^2 and R^5 are as previously defined for formula (I). Similarly, compounds of formula (III) and (IIIA) are key intermediates for the preparation of (IA).

The compound of formula (II) may be prepared as shown in Scheme 1 below, wherein R^1, R^2 and R^5 are as previously defined. Within the definition of formula (II) compounds of formula (III) and (IIIA) are included. Thus, in these cases, suitable protection as previously described may be utilised throughout. For example, the definition of R^5 for compounds (VII), (VIII), (IX), (X), (XI) may include P^5, which may include a formamidine group.



Scheme 1

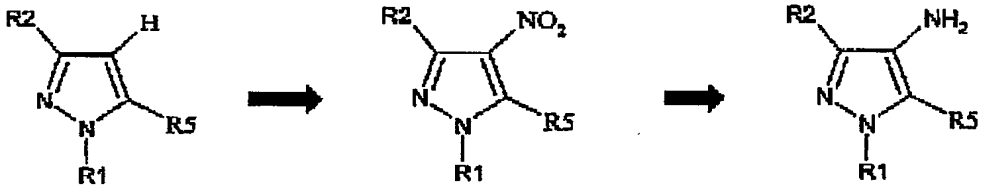
A compound of formula (X) may be obtained from a compound of formula (XI) by conventional halogenation procedures. For example, when 'halo' is iodo, (X) is treated with *N*-iodosuccinimide in a suitable solvent such as acetonitrile at from about room temperature to about 85 ° C. (X) may be carbonylated using conventional procedures, for example, using a palladium catalyst. Typically a solution of (X), triethylamine and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II).dichloromethane in methanol is heated at temperatures ranging from 55°C to 65°C under carbon monoxide (at pressures ranging from 125 – 175psi) for several hours, typically 8 hours.

Saponification of the methyl ester, (IX), to give the acid, (VIII), may be achieved using standard ester hydrolysis conditions. A particularly useful procedure involves refluxing a pyridine solution of (IX) and lithium iodide, under an inert atmosphere for 15 – 25 hours followed by stirring at room temperature for an extended time, typically 50 hours. (VII) may be prepared from (VIII) by the Curtius rearrangement

of the acyl azide prepared *in situ* by conventional procedures. For example, diphenylphosphoryl azide is added dropwise to a solution of (VIII), triethylamine and 2-(trimethylsilyl)ethanol in 1,4-dioxane. Refluxing for 10 – 25 hours, typically overnight yields the protected amine (VII). Deprotection to yield (II) may be effected using a variety of fluoride induced desilylation procedures, such as heating a solution of (VII) and tetrabutylammonium fluoride in a suitable solvent, typically tetrahydrofuran, at temperatures ranging from 45-55°C for 0.5-5 hours.

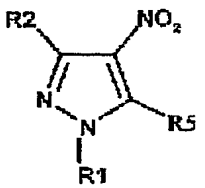
An alternative route to compounds of formula (II) is via nitration of (XI) to give (XII) followed by reduction of the C4-nitro substituent of (XII) to the amine (II) as shown in Scheme 2, wherein R^1, R^2 and R^5 are as previously defined. As described earlier, within the definition of formula (II) compounds of formula (III) and (IIIA) are included. Thus, in these cases, suitable protection as previously described may be utilised for (XI) and (XII). For example, in Scheme 2 the definition of R^5 may include P^5, which may include a formamidine group.

Scheme 2



(XI) (XII) (II)

The preparation of (XII) may be effected by conventional electrophilic nitration procedures, typically stirring a solution of (XI) and nitronium tetrafluoroborate in a suitable solvent, such as acetonitrile at room temperature for several, typically 2, hours.

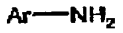


(XII)

wherein R^1, R^2 and R^5 are as previously defined for formula (I). Reduction of (XII) may be facilitated by a variety of reducing agents including those described in "Handbook of Reagents for Organic Synthesis – Oxidising and Reducing Agents" edited by S.D.Burke and R.L.Danheiser. Examples include metal catalysed hydrogenation procedures typically shaking a methanolic solution of (XII) under an atmosphere of hydrogen, at 50psi, using a 5% platinum on charcoal catalyst.

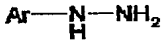
Synthesis of the arylpyrazole template can be readily performed.

A 1-aminobenzene or 1-aminopyridine such as (XIII) undergoes diazotisation by reaction with sodium nitrite in an acidic mixture, for example glacial acetic acid and sulphuric acid at temperatures between 5 – 60°C.



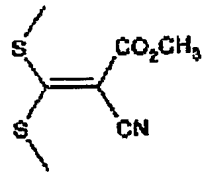
(XIII)

From a compound of formula (XIII) the hydrazine (XIV) can be obtained by reduction with an agent such as tin (II) chloride in a concentrated acid such as hydrochloric acid.

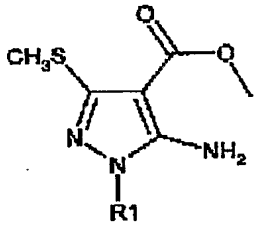


(XIV)

Hydrazine (XIV) may treated with an electrophile such as compound (XV) in an aprotic solvent such as isopropyl alcohol at reflux for several hours to give a functionalised arylpyrazole such as (XVI)



(XV)

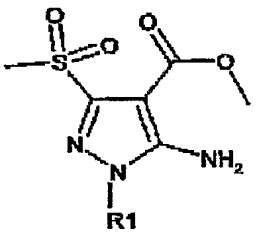


(XVI)

Compound (XVI), wherein R^1 is as previously defined for compounds of formula (I), may be transformed into compounds of formula (I) using the methodology

described above, e.g. protection of the amino functionality, for example, with *N,N*-dimethylformamide dimethylacetal; saponification using standard mild conditions such as treatment with lithium iodide in an aprotic solvent such as pyridine at elevated temperature; the acid may be rearranged using Curtius methodology in the presence of diphenylphosporyl azide and 2-(trimethylsilyl)ethanol; deprotection of the resultant amine then permits *mono*- and *bis*-sulphonylation, alkylation and other reactions as described above.

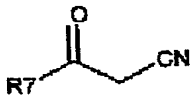
Alternatively, thioether (XVI) may be oxidised using standard oxidising conditions to give compounds such as (XVII). Illustrative oxidising conditions may include treatment with *m*-chloroperoxybenzoic acid in an aprotic solvent such as dichloromethane at temperatures between 0-25°C for several hours.



(XVII)

Compound (XVII), wherein R^1 is as previously described, may be transformed into compounds of formula (I) using the methodology described above, e.g. protection of the amino functionality perhaps with *N,N*-dimethylformamide dimethylacetal; saponification using standard mild conditions such as treatment with lithium iodide in an aprotic solvent such as pyridine at elevated temperature; the acid may be rearranged using Curtius methodology in the presence of diphenylphosporyl azide and 2-(trimethylsilyl)ethanol; deprotection of the resultant amine then permits *mono*- and *bis*-sulphonylation, alkylation and other reactions as described above.

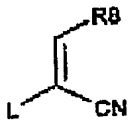
Similarly hydrazine (XIV) may be reacted with α-cyanoketones such as (XVIII) wherein R^7 may be C_{1-6} alkyl optionally substituted by halo and C_3 to C_8 cycloalkyl, at elevated temperatures to produce compounds of formula (XI) wherein R^2 may be C_{1-6} alkyl optionally substituted by halo and C_3 to C_8 cycloalkyl.



(XVIII)

For example, when R^7 is cyclopropyl, compounds (XVII) where R^2 is cyclopropyl, can be obtained by heating (XVIII) and hydrazine (XIV) together in a protic solvent such as propanol for several hours.

Hydrazine (XIV) may also be reacted with acrylonitriles such as (XIX), wherein R^8 may be hydrogen, C_{1-6} alkyl optionally substituted by halo and C_3 to C_8 cycloalkyl, and L is a leaving group such as chloro, bromo, iodo. At elevated temperatures compounds of formula (XI) wherein R^2 may be hydrogen, C_{1-6} alkyl optionally substituted by halo and C_3 to C_8 cycloalkyl are produced.

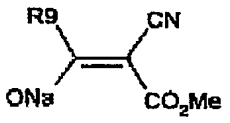


(XIX)

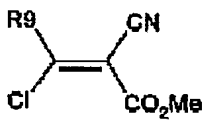
For example, when (XIX) is 2-chloroacrylonitrile, reaction with hydrazine (XIV) in methanol in the presence of diaminotetraacetic acid disodium at reflux gave formula (XI) where R^2 is hydrogen.

Similarly hydrazine (XIV) may be reacted with functionalised alkenes such as (XXI) wherein R^9 may be C_{1-6} alkyl optionally substituted by halo, C_3 to C_8 cycloalkyl and cyano, in aprotic solvents such as diethyl ether in the presence of a mild base such as potassium carbonate to give compounds of formula (IX).

Chloroalkenes (XXI) are obtained by chlorination of alkenes (XX) using phosphorous pentachloride in a solvent such as dichloromethane at room temperature.



(XX)



(XXI)

Functionalised alkenes (XX) may be synthesised using a wide variety of literature methodology.

Moreover, persons skilled in the art will be aware of variations of, and alternatives to, the processes described which allow the compounds defined by formula (I) to be obtained.

It will also be appreciated by persons skilled in the art that, within certain of the processes described, the order of the synthetic steps employed may be varied and will depend *inter alia* on factors such as the nature of other functional groups present in a particular substrate, the availability of key intermediates, and the protecting group strategy (if any) to be adopted. Clearly, such factors will also influence the choice of reagent for use in the said synthetic steps. It will also be appreciated that various standard substituent or functional group interconversions and transformations within certain compounds of formula (I) will provide other compounds of formula (I).

The skilled person will appreciate that the compounds of the invention could be made by methods other than those herein described, by adaptation of the methods herein described and/or adaptation of methods known in the art, for example the art described herein, or using standard textbooks such as "Comprehensive Organic Transformations - A Guide to Functional Group Transformations", RC Larock, Wiley-VCH (1999 or later editions), "March's Advanced Organic Chemistry - Reactions, Mechanisms and Structure", MB Smith, J. March, Wiley, (5th edition or later) "Advanced Organic Chemistry, Part B, Reactions and Synthesis", FA Carey, RJ Sundberg, Kluwer Academic/Plenum Publications, (2001 or later editions), "Organic Synthesis - The Disconnection Approach", S Warren (Wiley), (1982 or later editions), "Designing Organic Syntheses" S Warren (Wiley) (1983 or

later editions), "Guidebook To Organic Synthesis" RK Mackie and DM Smith (Longman) (1982 or later editions), etc.,and the references therein as a guide.

It is to be understood that the synthetic transformation methods mentioned herein are exemplary only and they may be carried out in various different sequences in order that the desired compounds can be efficiently assembled. The skilled chemist will exercise his judgement and skill as to the most efficient sequence of reactions for synthesis of a given target compound. For example, substituents may be added to and/or chemical transformations performed upon, different intermediates to those mentioned hereinafter in conjunction with a particular reaction. This will depend *inter alia* on factors such as the nature of other functional groups present in a particular substrate, the availability of key intermediates and the protecting group strategy (if any) to be adopted. Clearly, the type of chemistry involved will influence the choice of reagent that is used in the said synthetic steps, the need, and type, of protecting groups that are employed, and the sequence for accomplishing the synthesis. The procedures may be adapted as appropriate to the reactants, reagents and other reaction parameters in a manner that will be evident to the skilled person by reference to standard textbooks and to the examples provided hereinafter.

It will be apparent to those skilled in the art that sensitive functional groups may need to be protected and deprotected during synthesis of a compound of the invention. This may be achieved by conventional methods, for example as described in "Protective Groups in Organic Synthesis" by TW Greene and PGM Wuts, John Wiley & Sons Inc (1999), and references therein.

Pharmaceutically acceptable salts of the compounds of formula (I) include the acid addition and base salts thereof for compounds of sufficient acidity or basisity.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide,

hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

A pharmaceutically acceptable salt of a compound of formula (I) may be readily prepared by mixing together solutions of the compound of formula (I) and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the salt may vary from completely ionised to almost non-ionised.

The compounds of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionised, partially ionised, or non-

ionised. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Haleblian (August 1975).

Hereinafter all references to compounds of formula (I) include references to salts, solvates and complexes thereof and to solvates and complexes of salts thereof.

The compounds of the invention include compounds of formula (I) as hereinbefore defined, and all polymorphs and prodrugs thereof. The invention also includes all isomers of the compounds of formula (I) (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labeled compounds of formula (I).

Also within the scope of the invention are so-called 'prodrugs' of the compounds of formula (I) as mentioned above. Thus certain derivatives of compounds of formula (I) which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of formula (I) having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in 'Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T Higuchi and W Stella) and 'Bioreversible Carriers in Drug Design', Pergamon Press, 1987 (ed. E B Roche, American Pharmaceutical Association).

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of formula (I) with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in "Design of Prodrugs" by H Bundgaard (Elsevier, 1985).

Some examples of prodrugs include:

(i) where the compound of formula (I) contains a carboxylic acid functionality (-COOH), an ester thereof, for example, replacement of the hydrogen with (C_1-C_8 alkyl;

(ii) where the compound of formula (I) contains an alcohol functionality (-OH), an ether thereof, for example, replacement of the hydrogen with (C_1-C_6)alkanoyloxymethyl; and

(iii) where the compound of formula (I) contains a primary or secondary amino functionality (-NH_2 or -NHR where R ≠ H), an amide thereof, for example, replacement of one or both hydrogens with (C_1-C_{10})alkanoyl.

Further examples of replacement groups in accordance with the foregoing examples and examples of other prodrug types may be found in the aforementioned references.

Finally, certain compounds of formula (I) may themselves act as prodrugs of other compounds of formula (I).

Compounds of formula (I) containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where a compound of formula (I) contains an alkenyl or alkenylene group, geometric *cis/trans* (or Z/E) isomers are possible. Where the compound contains, for example, a keto or oxime group or an aromatic moiety, tautomeric isomerism ('tautomerism') can occur. It follows that a single compound may exhibit more than one type of isomerism.

Included within the scope of the present invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of formula (I), including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base salts wherein the counterion is optically active, for example, D-lactate or L-lysine, or racemic, for example, DL-tartrate or DL-arginine.

Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallisation.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the

racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula (I) contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% isopropanol, typically from 2 to 20%, and from 0 to 5% of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

Stereoisomeric conglomerates may be separated by conventional techniques known to those skilled in the art - see, for example, "Stereochemistry of Organic Compounds" by E L Eliel (Wiley, New York, 1994).

The present invention includes all pharmaceutically acceptable isotopically-labelled compounds of formula (I) wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S.

Certain isotopically-labelled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g. D_2O, d_6-acetone, d_6-DMSO. Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

They may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof).

Compounds of this invention can also be mixed with one or more biologically active compounds or agents including insecticides, acaricides, anthelmintics,

fungicides, nematocides, antiprotozoals, bactericides, growth regulators, entomopathogenic bacteria, viruses or fungi to form a multi-component pesticide giving an even broader spectrum of pharmaceutical, veterinary or agricultural utility. Thus the present invention also pertains to a composition comprising a biologically effective amount of compounds of the invention and an effective amount of at least one additional biologically active compound or agent and can further comprise one or more of surfactant, a solid diluent or a liquid diluent.

The following list of biologically active compounds together with which the compounds of the invention can be used is intended to illustrate the possible combinations, but not to impose any limitation.

For example, compounds of the present invention may be co-administered or used in combination with anthelmintic agents. Such anthelmintic agents include, compounds selected from the macrocyclic lactone class of compounds such as ivermectin, avermectin, abamectin, emamectin, eprinomectin, doramectin, selamectin, moxidectin, nemadectin and milbemycin derivatives as described in EP-357460, EP-444964 and EP-594291. Additional anthelmintic agents include semisynthetic and biosynthetic avermectin/milbemycin derivatives such as those described in US-5015630, WO-9415944 and WO-9522552. Additional anthelmintic agents include the benzimidazoles such as albendazole, cambendazole, fenbendazole, flubendazole, mebendazole, oxfendazole, oxibendazole, parbendazole, and other members of the class. Additional anthelmintic agents include imidazothiazoles and tetrahydropyrimidines such as tetramisole, levamisole, pyrantel pamoate, oxantel or morantel.

Compounds of this invention may also be used in combination with derivatives and analogues of the paraherquamide/marcfortine class of anthelmintic agents, as well as the antiparasitic oxazolines such as those disclosed in US-5478855, US-4639771 and DE-19520936.

Compounds of this invention may be co-administered or used in combination with derivatives and analogues of the general class of dioxomorpholine antiparasitic

agents as described in WO-9615121 and also with anthelmintic active cyclic depsipeptides such as those described in WO-9611945, WO-9319053, WO-9325543, EP-626375, EP-382173, WO-9419334, EP-382173, and EP-503538.

Compounds of this invention may be co-administered or used in combination with other ectoparasiticides; for example, fipronil; pyrethroids; organophosphates; insect growth regulators such as lufenuron; ecdysone agonists such as tebufenozide and the like; neonicotinoids such as imidacloprid and the like.

Other examples of such biologically active compounds include but are not restricted to the following:

Organophosphates: acephate, azamethiphos, azinphos-ethyl, azinphos-methyl, bromophos, bromophos-ethyl, cadusafos, chlorethoxyphos, chlorpyrifos, chlorfenvinphos, chlormephos, demeton, demeton-S-methyl, demeton-S-methyl sulphone, dialifos, diazinon, dichlorvos, dicrotophos, dimethoate, disulfoton, ethion, ethoprophos, etrimfos, famphur, fenamiphos, fenitrothion, fensulfothion, fenthion, flupyrazofos, fonofos, formothion, fosthiazate, heptenophos, isazophos, isothioate, isoxathion, malathion, methacriphos, methamidophos, methidathion, methyl-parathion, mevinphos, monocrotophos, naled, omethoate, oxydemeton-methyl, paraoxon, parathion, parathion-methyl, phenthoate, phosalone, phosfolan, phosphocarb, phosmet, phosphamidon, phorate, phoxim, pirimiphos, pirimiphos-methyl, profenofos, propaphos, proetamphos, prothiofos, pyraclofos, pyridapenthion, quinalphos, sulprophos, temephos, terbufos, tebupirimfos, tetrachlorvinphos, thimeton, triazophos, trichlorfon, vamidothion.

Carbamates: alanycarb, aldicarb, 2-sec-butylphenyl methylcarbamate, benfuracarb, carbaryl, carbofuran, carbosulfan, cloethocarb, ethiofencarb, fenoxycarb, fenthiocarb, furathiocarb, HCN-801, isoprocarb, indoxacarb, methiocarb, methomyl, 5-methyl-m-cumenylbutyryl(methyl)carbamate, oxamyl, pirimicarb, propoxur, thiodicarb, thiofanox, triazamate, UC-51717

Pyrethroids: acrinathin, allethrin, alphametrin, 5-benzyl-3-furylmethyl (E) – (1R)-cis-2,2-dimethyl-3-(2-oxothiolan-3-ylidenemethyl)cyclopropanecarboxylate, bifenthrin, β-cyfluthrin, cyfluthrin, α-cypermethrin, β-cypermethrin, bioallethrin, bioallethrin((S)-cyclopentylisomer), bioresmethrin, bifenthrin, NCI-85193, cycloprothrin, cyhalothrin, cythithrin, cyphenothrin, deltamethrin, empenthrin, esfenvalerate, ethofenprox, fenfluthrin, fenpropathrin, fenvalerate, flucythrinate, flumethrin, fluvalinate (D isomer), imiprothrin, cyhalothrin, λ-cyhalothrin, permethrin, phenothrin, prallethrin, pyrethrins (natural products), resmethrin, tetramethrin, transfluthrin, theta-cypermethrin, silafluofen, τ-fluvalinate, tefluthrin, tralomethrin, Zeta-cypermethrin.

Arthropod growth regulators: a) chitin synthesis inhibitors: benzoylureas: chlorfluazuron, diflubenzuron, fluazuron, flucycloxuron, flufenoxuron, hexaflumuron, lufenuron, novaluron, teflubenzuron, triflumuron, buprofezin, diofenolan, hexythiazox, etoxazole, chlorfentazine; b) ecdysone antagonists: halofenozide, methoxyfenozide, tebufenozide; c) juvenoids: pyriproxyfen, methoprene, fenoxycarb; d) lipid biosynthesis inhibitors: spirodiclofen

Other antiparasitics: acequinocyl, amitraz, AKD-1022, ANS-118, azadirachtin, Bacillus thuringiensis, bensultap, bifenazate, binapacryl, bromopropylate, BTG-504, BTG-505, camphechlor, cartap, chlorobenzilate, chlordimeform, chlorfenapyr, chromafenozide, clothianidine, cyromazine, diacloden, diafenthiuron, DBI-3204, dinactin, dihydroxymethyldihydroxypyrrolidine, dinobuton, dinocap, endosulfan, ethiprole, ethofenprox, fenazaquin, flumite, MTI-800, fenpyroximate, fluacrypyrim, flubenzimine, flubrocythrinate, flufenzine, flufenprox, fluproxyfen, halofenprox, hydramethylnon, IKI-220, kanemite, NC-196, neem guard, nidinorterfuran, nitenpyram, SD-35651, WL-108477, pirydaryl, propargite, protrifenbute, pymethrozine, pyridaben, pyrimidifen, NC-1111, R-195, RH-0345, RH-2485, RYI-210, S-1283, S-1833, SI-8601, silafluofen, silomadine, spinosad, tebufenpyrad, tetradifon, tetranactin, thiacloprid, thiocyclam, thiamethoxam, tolfenpyrad, triazamate, triethoxyspinosyn, trinactin, verbutin, vertalec, YI-5301

Fungicides: acibenzolar, aldimorph, ampropylfos, andoprim, azaconazole, azoxystrobin, benalaxyl, benomyl, bialaphos, blasticidin-S, Bordeaux mixture, bromuconazole, bupirimate, carpropamid, captafol, captan, carbendazim, chlorfenazole, chloroneb, chloropicrin, chlorothalonil, chlozolinate, copper oxychloride, copper salts, cyflufenamid, cymoxanil, cyproconazole, cyprodinil, cyprofuram, RH-7281, diclocymet, diclobutrazole, diclomezine, dicloran, difenoconazole, RP-407213, dimethomorph, domoxystrobin, diniconazole, diniconazole-M, dodine, edifenphos, epoxiconazole, famoxadone, fenamidone, fenarimol, fenbuconazole, fencaramid, fenpiclonil, fenpropidin, fenpropimorph, fentin acetate, fluazinam, fludioxonil, flumetover, flumorf/flumorlin, fentin hydroxide, fluoxastrobin, fluquinconazole, flusilazole, flutolanil, flutriafol, folpet, fosetyl-aluminium, furalaxyl, furametapyr, hexaconazole, ipconazole, iprobenfos, iprodione, isoprothiolane, kasugamycin, krsoxim-methyl, mancozeb, maneb, mefenoxam, mepronil, metalaxyl, metconazole, metominostrobin/fenominostrobin, metrafenone, myclobutanil, neo-asozin, nicobifen, orysastrobin, oxadixyl, penconazole, pencycuron, probenazole, prochloraz, propamocarb, propioconazole, proquinazid, prothioconazole, pyrifenox, pyraclostrobin, pyrimethanil, pyroquilon, quinoxyfen, spiroxamine, sulfur, tebuconazole, tetrconazole, thiabendazole, thifluzamide, thiophanate-methyl, thiram, tiadinil, triadimefon, triadimenol, tricyclazole, trifloxystrobin, triticonazole, validamycin, vinclozin

Biological agents: Bacillus thuringiensis ssp aizawai, kurstaki, Bacillus thuringiensis delta endotoxin, baculovirus, entomopathogenic bacteria, virus and fungi

Bactericides: chlortetracycline, oxytetracycline, streptomycin,

Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term "excipient" is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. The compounds of the invention are of particular value in the

control of parasites which are injurious to, or spread or act as vectors of diseases in, man and domestic animals, for example those hereinbefore mentioned, and more especially in the control of ticks, mites, lice, fleas, midges and biting, nuisance and myiasis flies. They are particularly useful in controlling arthropods which are present inside domestic host animals or which feed in or on the skin or suck the blood of the animal, for which purpose they may be administered orally, parenterally, percutaneously or topically.

Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in 'Remington's Pharmaceutical Sciences', 19th Edition (Mack Publishing Company, 1995).

With respect to their use in mammals, the compounds may be administered alone or in a formulation appropriate to the specific use envisaged, the particular species of host mammal being treated and the parasite involved.

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films (including muco-adhesive), ovules, sprays and liquid formulations.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986 by Liang and Chen (2001).

For tablet dosage forms, depending on dose, the drug may make up from 1 wt% to 80 wt% of the dosage form, more typically from 5 wt% to 60 wt% of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 wt% to 25 wt%, preferably from 5 wt% to 20 wt% of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 wt% to 5 wt% of the tablet, and glidants may comprise from 0.2 wt% to 1 wt% of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 wt% to 10 wt%, preferably from 0.5 wt% to 3 wt% of the tablet.

Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 wt% to about 90 wt% binder, from about 0 wt% to about 85 wt% diluent, from about 2 wt% to about 10 wt% disintegrant, and from about 0.25 wt% to about 10 wt% lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tabletting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated.

The formulation of tablets is discussed in "Pharmaceutical Dosage Forms: Tablets, Vol. 1", by H. Lieberman and L. Lachman, Marcel Dekker, N.Y., N.Y., 1980 (ISBN 0-8247-6918-X).

Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Verma *et al*, Pharmaceutical Technology On-line, 25(2), 1-14 (2001).

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include bolus, intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of formula (I) used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and PGLA microspheres.

The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include drenches, gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958 by Finnin and Morgan (October 1999). Pour-on or spot-on formulations may be prepared by dissolving the active ingredient in an acceptable liquid carrier vehicle such as butyl digol, liquid paraffin or a non-volatile ester, optionally with the addition of a volatile component such as propan-2-ol. Alternatively, pour-on, spot-on or spray

formulations can be prepared by encapsulation, to leave a residue of active agent on the surface of the animal. Injectable formulations may be prepared in the form of a sterile solution which may contain other substances, for example enough salts or glucose to make the solution isotonic with blood.

Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (*e.g.* Powderject™, Bioject™, *etc.*) injection.

Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

Capsules (made, for example, from gelatin or HPMC), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as *l*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1µg to 20mg of the compound of the invention per actuation and the actuation volume may vary from 1µl to 100µl. A typical formulation may comprise a compound of formula (I), propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, poly(DL-lactic-coglycolic acid (PGLA). Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing from 1 to 1000 µg of the compound of formula (I). The overall daily dose will typically be in the range 100 µg to 100 mg which may be administered in a single dose or, more usually, as divided doses throughout the day.

The compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (*e.g.* absorbable gel sponges, collagen) and non-biodegradable (*e.g.* silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

Formulations for ocular/aural administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted, or programmed release.

The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

Acceptable liquid carriers include vegetable oils such as sesame oil, glycerides such as triacetin, esters such as benzyl benzoate, isopropyl myristate and fatty acid derivatives of propylene glycol, as well as organic solvents such as pyrrolidin-2-one and glycerol formal. The formulations are prepared by dissolving or suspending the active ingredient in the liquid carrier such that the final formulation contains from 0.01 to 10% by weight of the active ingredient.

Such formulations are prepared in a conventional manner in accordance with standard medicinal or veterinary practice.

These formulations will vary with regard to the weight of active compound contained therein, depending on the species of host animal to be treated, the severity and type of infection and the body weight of the host. For parenteral, topical and oral administration, typical dose ranges of the active ingredient are 0.01 to 100 mg per kg of body weight of the animal. Preferably the range is 0.1 to 10mg per kg.

As an alternative the compounds may be administered to a non-human animal with the drinking water or feedstuff and for this purpose a concentrated feed additive or premix may be prepared for mixing with the normal animal feed or drink.

Inasmuch as it may desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions.

Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of formula (I) in accordance with the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An

example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

For administration to animal patients, the total daily dose of the compounds of the invention is typically in the range 0.1 mg/kg to 100 mg/kg depending, of course, on the mode of administration. For example, oral administration may require a total daily dose of from 0.5 mg/kg to 100 mg/kg, while an intravenous dose may only require from 0.1 mg/kg to 10 mg/kg. The total daily dose may be administered in single or divided doses. The veterinarian will readily be able to determine doses for individual animals according to age, weight and need.

The compounds of the invention also have utility in the control of plant pests, soil inhabiting pests and other environmental pests.

Compositions suitable for applications in agriculture, horticulture include formulations suitable for use as, for example, sprays, dusts, granules, fogs, foams, emulsions. The active compound is generally applied to the locus in which arthropod or nematode infestation is to be controlled at a rate of about 0.02 kg to about 20 kg of active compound per hectare of locus treated. Adverse weather conditions, pest resistance and other factors may require that the active ingredient be used in higher proportions. For foliar application, a rate of 0.01 to 1 kg/ha may be used.

The compounds of the invention may also be applied in solid or liquid compositions to the soil principally to control those nematodes dwelling therein but also to the foliage principally to control those nematodes attacking the aerial parts of the plants. The active component can be washed into the soil by spraying with

water or by the natural action of rainfall. During or after application, the formulation can, if desired, be distributed mechanically in the soil.

Application can be prior to planting, at planting, after planting but before sprouting has taken place or after sprouting.

The compounds of the invention are of particular value in the protection of field, grassland, forage, plantation, glasshouse, orchard, grove and vineyard crops; or of vegetables and salds, of ornamental plants flowers and shrubs and of plantation and forest trees.

The effective use doses of the compounds employed in the invention can vary within wide limits, particularly depending on the nature of the pest to be eliminated or degree of infestation. In general, the compositions according to the invention usually contain about 0.05 to about 95% (by weight) of one or more active ingredients according to the invention, about 1 to about 95% of one or more solid or liquid carriers and, optionally, about 0.1 to about 50% of one or more other compatible components, such as surface-active agents or the like.

In the present account, the term "carrier" denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate its application. This carrier is therefore generally inert and it must be acceptable (for example, agronomically acceptable, particularly to the treated plant).

The carrier may be a solid, for example, ground natural minerals, such as attapulgite, bentonite, clays, chalk, diatomaceous earth, kaolins, montmorillonite, quartz, or talc, ground synthetic minerals, such as alumina, silica, or silicates, naturalsilicates, silica, resins, waxes, or solid fertilizers). As solid carriers for granules the following are suitable: crushed natural rocks such as calcite, dolomite, marble, pumice, and sepiolite; synthetic granules of inorganic or organic meals; granules of organic material such as, coconut shells, corn cobs, corn husks or sawdust; absorbent carbon black, kieselguhr, or powdered cork; water soluble polymers, resins, waxes; or solid fertilizers. Such solid compositions may, if

desired, contain one or more compatible wetting, dispersing, emulsifying or colouring agents which, when solid, may also serve as a diluent.

The carrier may also be liquid, for example: water; alcohols, particularly butanol or glycol, as well as their ethers or esters, particularly methyl glycol acetate; ketones, particularly acetone, cyclohexanone, methylethyl ketone, methylisobutylketone, or isophorone; petroleum fractions such as aliphatic or aromatic hydrocarbons, particularly xylenes; mineral or vegetable oils; chlorinated hydrocarbons, particularly trichloroethane,methylene chloride or chlorobenzenes; water-soluble or strongly polar solvents such as dimethylformamide, dimethyl sulphoxide, or N-methylpyrrolidone; or a mixture thereof.

The surface-active agent may be an emulsifying agent, dispersing agent or wetting agent of the ionic or non-ionic type or a mixture of such agents. The presence of at least one surface-active agent is generally essential when the active ingredient and/or the inert carrier are not or only slightly water soluble and the carrier agent of the composition for application is water.

Compositions of the invention may further contain other additives such as adhesives or colorants. Adhesives such as natural or synthetic phospholipids or carboxymethylcellulose or natural or synthetic polymers in the form of powders, granules or lattices, can be used in the formulations. It is possible to use colorants such as inorganic pigments, for example: iron oxides, titanium oxides or Prussian Blue; organic dyestuffs, such as alizarin dyestuffs, azo dyestuffs or metal phthalocyanine dyestuffs; or It is also possible to use trace nutrients such as salts of boron, cobalt, iron, manganese, copper, cobalt, molybdenum or zinc.

For their agricultural application, the compounds of the formula (I), or pesticidally acceptable salts thereof, are therefore generally in the form of compositions, which are in various solid or liquid forms.

Solid forms of compositions which can be used are dusting powders (with a content of the compound of formula (I), or a pesticidally acceptable salt thereof, ranging up to 80%), wettable powders or granules (including water dispersible

granules), particularly those obtained by extrusion, compacting, impregnation of a granular carrier, or granulation starting from a powder (the content of the compound of formula (I), or a pesticidally acceptable salt thereof, in these wettable powders or granules being between about 0.5 and about 80%). Solid homogenous or heterogenous compositions containing one or more compounds of formula (I), or pesticidally acceptable salts thereof, for example granules, pellets, briquettes or capsules, may be used to treat standing or running water over a period of time. A similar effect may be achieved using trickle or intermittent feeds of water dispersible concentrates as described herein.

Liquid compositions, for example, include aqueous or non-aqueous solutions or suspensions (such as emulsifiable concentrates, emulsions, flowables, dispersions, or solutions) or aerosols. Liquid compositions also include, in particular, emulsifiable concentrates, dispersions, emulsions, flowables, aerosols, wettable powders (or powder for spraying), dry flowables or pastes as forms of compositions which are liquid or intended to form liquid compositions when applied, for example as aqueous sprays (including low and ultra-low volume) or as fogs or aerosols.

Liquid compositions, for example, in the form of emulsifiable or soluble concentrates most frequently comprise about 5 to about 80% by weight of the active ingredient, while the emulsions or solutions which are ready for application contain, in their case, about 0.0 1 to about 20% of the active ingredient. Besides the solvent, the emulsifiable or soluble concentrates may contain, when required, about 2 to about 50% of suitable additives, such as stabilizers, surface-active agents, penetrating agents, corrosion inhibitors, colorants or adhesives. Emulsions of any required concentration, which are particularly suitable for application, for example, to plants, may be obtained from these concentrates by dilution with water. These compositions are included within the scope of the compositions which may be employed in the present invention. The emulsions may be in the form of water-in-oil or oil-in-water type and they may have a thick consistency.

The liquid compositions of this invention may, in addition to normal agricultural use applications be used for example to treat substrates or sites infested or liable to

infestation by arthropods (or other pests controlled by compounds of this invention) including premises, outdoor or indoor storage or processing areas, containers or equipment or standing or running water.

All these aqueous dispersions or emulsions or spraying mixtures can be applied, for example, to crops by any suitable means, chiefly by spraying, at rates which are generally of the order of about 100 to about 1,200 liters of spraying mixture per hectare, but may be higher or lower (eg.low or ultra-low volume) depending upon the need or application technique. The compounds or compositions according to the invention are conveniently applied to vegetation and in particular to roots or leaves having pests to be eliminated. Another method of application of the compounds or compositions according to the invention is by chemigation, that is to say, the addition of a formulation containing the active ingredient to irrigation water. This irrigation may be sprinkler irrigation for foliar pesticides or it can be ground irrigation or underground irrigation for soil or for systemic pesticides.

The concentrated suspensions, which can be applied by spraying, are prepared so as to produce a stable fluid product which does not settle (fine grinding) and usually contain from about 10 to about 75% by weight of active ingredient, from about 0.5 to about 30% of surface-active agents, from about 0.1 to about 10% of thixotropic agents, from about 0 to about 30% of suitable additives, such as anti-foaming agents, corrosion inhibitors, stabilizers, penetrating agents, adhesives and, as the carrier, water or an organic liquid in which the active ingredient is poorly soluble or insoluble Some organic solids or inorganic salts may be dissolved in the carrier to help prevent settling or as antifreezes for water.

The wettable powers (or powder for spraying) are usually prepared so that they contain from about 10 to about 80% by weight of active ingredient, from about 20 to about 90% of a solid carrier, from about 0 to about 5% of a wetting agent, from about 3 to about 10% of a dispersing agent and, when necessary, from about 0 to about 80% of one or more stabilizers and/or other additives, such as penetrating agents, adhesives, anti-caking agents, colorants, or the like. To obtain these wettable powders, the active ingredient(s) is(are) thoroughly mixed in a suitable blender with additional substances which may be impregnated on the porous filler

and is(are) ground using a mill or other suitable grinder. This produces wettable powders, the wettability and the suspendability of which are advantageous. They may be suspended in water to give any desired concentration and this suspension can be employed very advantageously in particular for application to plant foliage.

The "water dispersible granules (WG)" (granules which are readily dispersible in water) have compositions which are substantially close to that of the wettable powders. They may be prepared by granulation of formulations described for the wettable powders, either by a wet route (contacting finely divided active ingredient with the inert filler and a little water, e.g. 1 to 20% by weight, or with an aqueous solution of a dispersing agent or binder, followed by drying and screening), or by a dry route (compacting followed by grinding and screening).

The rates and concentrations of the formulated compositions may vary according to the method of application or the nature of the compositions or use thereof. Generally speaking, the compositions for application to control arthropod, plant nematode, helminth or protozoan pests usually contain from about 0.00001 % to about 95%, more particularly from about 0.0005% to about 50% by weight of one or more compounds of formula (I), or pesticidally acceptable salts thereof, or of total active ingredients (that is to say the compound of formula (I), or a pesticidally acceptable salt thereof, together with: other substances toxic to arthropods or plant nematodes, anthelmintics, anticoccidials, synergists, trace elements or stabilizers). The actual compositions employed and their rate of application will be selected to achieve the desired effect(s) by the farmer, livestock producer, medical or veterinary practitioner, pest control operator or other person skilled in the art.

They are also valuable in the protection of timber (standing, felled, converted, stored or structural) from attack by sawflies or beetles or termites.They have applications in the protectiqn of stored products such as grains, fruits, nuts, spices and tobacco, whether whole, milled or compounded into products, from moth, beetle and mite attack. Also protected are stored animal products such as skins, hair, wool and feathers in natural or converted form (e.g. as carpets or textiles) from moth and beetle attack; also stored meat and fish from beetle, mite and fly attack. Solid or liquid compositions for application topically to timber, stored

products or household goods usually contain from about 0.00005% to about 90%, more particularly from about 0.001 % to about 10%, by weight of one or more compounds of formula (I) or pesticidally acceptable salts thereof.

The compounds of the invention (and their pharmaceutically, veterinarily and agriculturally acceptable salts) may be used, for example, in the following applications and on the following pests:

In the field of veterinary medicine or livestock husbandry or in the maintenance of public health against arthropods which are parasitic internally or externally upon vertebrates, particularly warm-blooded vertebrates, including man and domestic animals such as dogs, cats, cattle, sheep, goats, equines, swine, poultry and fish. Also, in the field of control of plant pests, soil inhabiting pests and other environmental pests. Illustrative of specific parasites which may be controlled by the compounds of this invention include arthropods such as:

Actinedida/Acaridida: chicken mite (Mesostigmata spp e.g. *Dermanyssus gallinae*); itch/scab mites (Sarcoptes spp e.g. *Sarcoptes scabiei*) mange mites (Psoroptes spp e.g. *Psoroptes ovis*, Chorioptes spp e.g. *Chorioptes bovis*); chiggers (Trombicula spp e.g. *Trombicula alfeddugesi*); Damalinia spp; Demodex spp; Acarapis spp; Cheyletiella spp; Ornithocheyletia spp; Myobia spp; Listrophorus spp; Acarus spp; Tyrophagus spp; Caloglyphus spp; Hypodectes spp; Pterolichus spp; Otodectes spp; Notoedres spp; Cytodites spp. Knemidocoptes spp; Laminiosioptes spp.

Siphonapterida: Ctenocephalides spp e.g. *Ctenocephalides canis*, *Ctenocephalides felis*; Xenopsylla spp e.g. *Xenopsylla cheopis*; Pulex spp e.g. *Pulex irritans*; Ceratophyllus spp.

Ticks: Argas spp e.g. *Argas persicus*; Ornithodorus spp e.g. *Ornithodorus moubata*; Otobius spp e.g. *Otobius megnini*; Ixodes spp e.g. *Ixodes ricinus, Ixodes rubicundus*; Amblyomma spp e.g. *Amblyomma americanum, Amblyomma variegatum*; Boophilus spp e.g. *Boophilus annulatus, Boophilus decoloratus,*

Boophilus microplus; Dermacentor spp e.g. *Dermacentor silvarum;* Haemophysalis spp; Hyalomma spp e.g. *Hyalomma truncatum;* Rhipicephalus spp e.g. *Rhipicephalus sanguineus, Rhipicephalus appendiculatus, Rhipicephalus evertsi;* Dermanyssus spp; Railletia spp; Pneumonyssus spp; Stemostoma spp; Varroa spp; and other ticks e.g. *Brevipalpus phoenicis, Bryobia praetiosa, Eotetranychus carpini, Eriophyes sheldoni, Paratetranychus pilosus, Phyllocoptruta oleivora, Polyphagotarsonemus latus, Tetranychus cinnabarinus, Tetranychus kanzawai, Tetranychus pacificus, Tetranychus telarius.*

Adult flies (Diptera): Horn fly (*Haematobia irritans*); Horse fly (Tabanus spp e.g. *Tabanus bovines*); Stable fly (*Stomoxys calcitrans*); Black fly (Simulium spp); Deer fly (Chrysops spp); Louse fly (*Melophagus ovinus*); Tsetse fly (Glossina spp e.g. *Glossina morsitans*); Mosquitoes (Culex spp e.g. *Culex pipiens*; Anopheles spp e.g. *Anopheles maculipennis*; Aedes spp e.g. *Aedes egypti, Aedes vexans*); Eusimulium spp; Phlebotonius spp; Lutzomyia spp; Culicoides spp; Hybomitra spp; Atylotus spp; Haematopota spp; Philipomyia spp; Braula spp; Hydrotaea spp; Morellia spp; Fannia spp e.g. *Fannia canucularis*; Calliphora spp; Wohlfahrtia spp; Sarcophaga spp; Hippobosca spp; Lipoptena spp; Melophagus spp; and other Diptera such as *Anastrepha ludens; Ceratitis capitata; Chrysomya bezziana; Chrysomya hominivorax; Chrysomya macellaria; Contarinia sorghicola; Cordylopia anthropophaga; Dacus cucurbitae; Dasineura brassicae; Gasterophilus intestinalis; Haplodiplosis equestris; Hylemyia platura; Hypoderma lineata; Liriomyza sativae; Liriomyza trifolii; Lycoria pectoralis; Mayettiola destructor; Musca domestica; Muscina stabulans; Oestrus ovis; Oscinella frit; Pegomya hysocyami; Phorbia brassicae; Phorbia coarctata; Rhagoletia cerasi; Rhagoletis pomonella; Tipula oleracearn; Tipula paludosa*; and also Blow flies; Soldierflies; Midges and Punkies.

Parasitic fly maggots: Bot fly (*Oestrus ovis*, Cuterebra spp); Blow fly (Phaenicia spp, *Lucilia sericata, Lucilia cuprina*); Screwworm (*Cochliomyia hominivorax*); Cattle grub (Hypoderma spp); *Dermatobia hominis*.

Anoplurida: sucking lice (Menopon spp; Bovicola spp); biting lice (Haematopinus spp; Linognathus spp; Solenoptes spp; Phtirus spp).

True bugs: common bed bug (Cimicidae e.g. *Cimex lectularius*); kissing bugs (Triatoma spp e.g. *Rhodnius prolixus*).

Brachycera: Black flies; Biting midges; Sand flies; Sciarids.

Orthoptera: Periplaneta spp; Blatella spp e.g. *Blatella germanica*; Gryllotalpa spp e.g. *Gryllotalpa gryllotalpa*; *Acheta domestica*; *Blatta orientalis* *Forficula auricularia*; *Leucophaea maderae*; *Melanoplus bivittatus*; *Melanoplus femur-rubrum*; *Melanoplus mexicanus*; *Melanoplus sanguinipes*; *Melanoplus spretus*; *Momadacris septemfasciata*; *Schistocerca peregrina*; *Stauronotus maroccanus*; *Tachycines asynamorus*.

Dictyoptera: *Periplaneta fuliginosa*; *Periplaneta japonica*; *Periplaneta Americana*.

Hymenoptera: Carpenter ants; Bees ; Hornets; Wasps.

Lepidoptera: *Adoxophyes orana fasciata*; *Agrotis ypsilon*; *Agrotis segetum*; *Alabama argillacea Hubner*; *Anticarsia gemmatalis*; *Archips argyrospila Walker*; *Archips rosana*; *Argyresthia conjugella*; *Autographa gamma*; *Autographa nigrisigna Barathra brassicae*; *Bupalus piniarius*; *Cacoecia murinana*; *Caloptilia theivora*; *Capua reticulana*; *Carposina niponensis*; *Cheimatobia brumata*; *Chilo polychrysus*; *Chilo suppressalis Walker*; *Choristoneura fumiferana*; *Choristoneura occidentalis*; *Cirphis unipuncta*; *Cnaphalocrosis medinalis Guenee*; *Cydia pomonella*; *Dendrolimus pini*; *Diaphania nitidalis*; *Diatraea grandiosella*; *Earias insulana Boisduval*; *Earias vittella Fabricius*; *Elasmopalpus lignosellus*; *Eupoecilia ambiguella*; *Evetria bouliana*; *Feltia subterrana*; *Galleria mellonella*; *Grapholitha funebrana*; *Grapholitha molesta*; *Helicoverpa armigera*; *Helicoverpa assulta*; *Helicoverpa zea*; *Heliothis virescens*; *Hellula undalis*; *Hibernia defoliaria*; *Hyphantria cunea*; *Hyponomeuta malinellus*; *Keiferia lycopersicella*; *Lambdina fiscellaria*; *Laphygma exigua*; *Leucoptera coffeella*; *Leucoptera scitella*; *Lithocolletis blancardella*; *Lobesia botrana*; *Loxostege sticticalis*; *Lymantria*

monacha; Lyonetia clerkella; Malacosoma neustria; Mamestra brassicae; Naranga aenescens; Notarcha derogata; Orgyia pseudotsugata; Ostrinia nubilalis; Ostrinia furnacalis; Pamara guttata; Panolis flammea; Pectinophora gossypiella; Peridroma saucia; Phalera bucephala; Phyllocnistis citrella; Pieris brassicae; Pieris rapae; Plutella xylostella; Pseudaletia separate; Phthorimaea operculella; Phyllonorycter ringoneella; Plathypena scabra; Pseudoplusia includens; Rhyacionia frustrana; Scrobipalpula absoluta; Sitotroga cerealella; Sparganothis pilleriana; Spodoptera exigua; Spodoptera frugiperda; Spodoptera littoralis; Spodoptera litura; Thaumatopoea pityocampa; Tortrix viridans; Trichoplusia ni Hubner; Tryporyza incertulas; Tuta absoluta; Zeiraphera Canadensis; Lyonetid moths; Tussock moths; Casemaking clothes moth; Webbing clothes moth.

Coleoptera: *Agrilus sinuatus; Agriotes lineatus; Agriotes obscurus; Amphimellus solstitialis; Anisandrus dispar; Anobium punctatum; Anoplophora malasiaca; Anthonomus grandis; Anthonomus pomorum; Anthrenus verbasci; Apate monachus; Atomaria linearis; Aulacophora femoralis; Blastophagus piniperda; Blitophaga undata; Bostrychos capucins; Bruchus rufimanus; Bruchus pisorum; Bruchis lentis; Byctiscus betulae; Callosobruchus chinensis; Cassida nebulosa; Cerotoma trifurcata; Ceuthorrhynchus assimilis; Ceuthorrhynchus napi; Chaetocnema tibialis; Chlorophorus pilosis; Conoderus vespertinus; Crioceris asparagi; Diabrotica longicornis; Dendrobium pertinex; Diabrotica 12-punctata; Diabrotica virgifera; Dinoderus minutes; Echinocnemus squameus; Elilachna vigintioctopunctata; Ernobius mollis; Epilachna varivestis; Epitrix hirtipennis; Eutinobothrus brasiliensis; Heterobostrychus brunneus; Hylobius abietis; Hylotrupes bajulus; Hypera brunneipennis; Hypera postica; Ips typographus; Lasioderma serricorne; Lema bilineata; Lema melanopus; Limonius californicus; Lissorhoptus oryzophilus; Lyctus brunneus; Lyctus linearis; Lyctus pubescens; Melanotus communis; Meligethes aeneus; Melolontha hippocastani; Melolontha melolontha; Minthes rugicollis; Oulema oryzae; Ortiorrhynchus sulcatus; Otiorrhynchus ovatus; Paederus fuscipes; Phaedon cochleariae; Phyllotreta chrysocephala; Phyllophaga spp; Phyllopertha horticola; Phyllotreta nemorum; Phyllotreta striotata; Popillia japonica; Priobium carpini; Ptilinus pecticornis; Sitona lineatus; Sitophilus granaria; Sphenophorus venatus; Tomicus piniperda; Tribolium castaneum; Trogoxylon aequale; Xestobium rufovillosum;* Aupreous chafer;

Western corn rootworm; Rice water weevil; Adzuki bean beetle; Yellow mealworm; Red flour beetle; Striped flea beetle; Cucurbit leaf beetle; Deathwatch beetle; Drugetose beetle; Mexican bean beetle; Flea beetle; Japanese beetle; Boll weevil; Rice water weevil; Granary weevil; Rice weevil; Wireworms (Agriotes spp; Athous spp; Limonius spp); *Xyleborus spp; Tryptodendron spp; Sinoxylon spp;*

Homoptera: *Acyrthosiphon onobrychis; Adelges laricis; Aleurodes brassicae; Aphidula nasturtii; Aphis fabae; Aphis gossypii; Aphis pomi; Aphis sambuci; Aspiodotus hederae; Bemisia tabaci; Bemisia argentifolii; Brachycaudus cardui; Brevicoryne brassicae; Cerosipha gossypii; Cryptomyzus ribis; Diuraphis noxia; Dreyfusia nordmannianae; Dreyfusia piceae; Dysaphis radicola; Dysaulacorthum pseudosolani; Empoasca fabae; Eriosoma lanigerum; Euscelis bilobatus; Hyalopterus arundinis; Laodelphax striatellus; Lecanium corni; Macrosiphum avenae; Macrosiphum euphorbiae; Macrosiphon rosae; Megoura viciae; Metolophium dirhodum; Myzodes persicae; Myzus cerasi; Myzus persicae; Nilaparvata lugens; Pemphigus bursarius; Perkinsiella saccharicida; Phorodon humuli; Psylla mali; Psylla piri; Rhopalomyzus ascalonicus; Rhopalosiphum maidis; Rhopalosiphum padi; Saissetia oleae; Sappaphis mala; Sappaphis mali; Schizaphis graminum; Schizoneura lanuginose; Sitobion avenae; Trialeurodes vaporariorum; Vites vitifolii.*

Hemiptera: *Aulacorthum solani; Aphis glycines; Eysarcoris parvus; Eurydema rugosum; Icerva purchasi; Laodelphax striatellus; Lipaphis erysimi; Nephotettix cincticeps; Planococcus citri; Pseudococcus comstocki; Riptortus clavatus; Scotinophora lurida; Sogatella furcifera; Stephanitis nashi; Unaspis yanonensis;* Small brown planthopper; Brown rice planthopper; Whitebacked rice planthopper; Stink bugs; Whiteflies; Lace bugs, Jumping plantlice.

And species of the orders: Hymenoptera; Isoptera; Isopoda; Diplopoda; Chilopoda; Symphyla; Thysanura; Dermaptera; and Heteroptera;

In the field of veterinary medicine or livestock husbandry or in the maintenance of public health for controlling helminths, nematodes and protozoa such as:

Trematoda: Fasciola; Fascioloides; Paramphistomum; Dicrocoelium; Eurytrema; Ophisthorchis; Fasciolopsis; Echinostoma; Paragonimus.

Nematodes: Haemonchus; Ostertagia; Cooperia; Oesphagastomum; Nematodirus; Dictyocaulus; Trichuris; Dirofilaria; Ancyclostoma; Ascaris; Trichostrongylus.

Protozoa: Eimeria spp; Leishmania spp; Plasmodium spp; Babesis spp; Trichomonadidae spp; Toxoplasma spp and Theileria spp.

In the protection of stored products, for example cereals, including grain or flour, groundnuts, animal feedstuffs, timber or household goods, e.g. carpets and textiles, compounds of the invention are useful against attack by arthropods such as:

Flour moths (Ephestia spp); Carpet beetles (Anthrenus spp); Flour beetles (Tribolium spp); Grain weevils (Sitophilus spp); Mites (Acarus spp)

In the protection against soil inhabiting insects such as:

Western corn rootworm, other Diabrotica spp, European chafer and other coleopteran grubs, and wireworms; adults and larvae of the orders Hemiptera and Homoptera including tarnished plant bug and other plant bugs (Miridae), aster leafhopper and other leaf hoppers (Cicadellidae), rice plant hopper, brown planthopper, and other planthoppers (Fulgoroidae), paylids, whiteflies (Aleurodidae), aphids (Aphidae), scales (Coccidae and Diaspididae), lace bugs (Tingidae), stink bugs (Pentamodidae), cinch bugs and other seed bugs (Lygaeidae), cicadas (Cicadidae), spittlebugs (Cercopids), squash bugs (Coreidae), red bugs and cotton stainers (Pyrrhocoridae); adults and larvae of the order acari including European red mite, two spotted mite, rust mites, McDaniel mite and other foliar feeding mites; adults and immatures of the order Orthoptera including grasshoppers; adults and immatures of the order Diptera including leafminers, midges, fruit flies (Tephritidae), and soil maggots; adults and

immatures of the order Thysanoptera including onion thrips and other foliar feeding thrips.

For the avoidance of doubt, references herein to "treatment" include references to curative, palliative and prophylactic treatment, references to "control" (of parasites and / or pests etc.) include kill, repel, expel, incapacitate, deter, eliminate, alleviate, minimise, eradicate.

The compounds of the invention are of particular value in the control of arthropods which are injurious to, or spread or act as vectors of diseases in, man and domestic animals, for example those hereinbefore mentioned, and more especially in the control of ticks, mites, lice, fleas, midges and biting, nuisance and myiasis flies. They are particularly useful in controlling arthropods which are present inside domestic host animals or which feed in or on the skin or suck the blood of the animal, for which purpose they may be administered orally, parenterally, percutaneously or topically.

Regarding the use of the compounds of the invention in mammals, there is provided:

a pharmaceutical or veterinary parasiticidal composition comprising a compound of formula (I), or a pharmaceutically or veterinarily acceptable salt thereof, or a pharmaceutically or veterinarily acceptable solvate of either entity, together with a pharmaceutically or veterinarily acceptable diluent or carrier, which may be adapted for oral, parenteral or topical administration;

a compound of formula (I), or a pharmaceutically or veterinarily acceptable salt thereof, or a pharmaceutically or veterinarily acceptable solvate of either entity, or a pharmaceutical or veterinary composition containing any of the foregoing, for use as a medicament;

the use of a compound of formula (I), or a pharmaceutically or veterinarily acceptable salt thereof, or a pharmaceutically or veterinarily acceptable solvate of

either entity, or a pharmaceutical or veterinary composition containing any of the foregoing, for the manufacture of a medicament for the treatment of a parasitic infestation; and

a method of treating a parasitic infestation in a mammal which comprises treating said mammal with an effective amount of a compound of formula (I), or a pharmaceutically or veterinarily acceptable salt thereof, or a pharmaceutically or veterinarily acceptable solvate of either entity, or a pharmaceutical or veterinarycomposition containing any of the foregoing.

According to another aspect of the present invention, there is provided a method for the control of arthropod, plant nematode or helminth pests at a locus which comprises the treatment of the locus (e.g. by application or administration) with an effective amount of a compound of general formula I, or a pesticidally acceptable salt thereof.

The present invention also relates to a method of cleaning animals in good health comprising the application to the animal of compound of formula (I) or a veterinarily acceptable salt. The purpose of such cleaning is to reduce or eliminate the infestation of humans with parasites carried by the animal and to improve the environment which humans inhabit.

The flea membrane feed test is used to measure the biological activities of the compounds claimed. The assay involves *in vitro* testing against *Ctenocephalides felis* conducted according to the following general procedure.

Fleas are cultured *in vitro* using dog blood. 25-30 adult *Ctenocephalides felis* (cat flea) were collected and placed in a test chamber (50ml polystyrene tube with fine nylon mesh sealing the end). Citrated dog blood was prepared by adding aqueous sodium citrate solution (10 ml, 20% w/v, 20g sodium citrate in 100 ml water) to dog blood (250 ml). Test compounds were dissolved in dimethylsulfoxide to give a working stock solution of 4 mg/ml. The stock solution (12.5 µl) was added to citrated dog blood (5 ml) to give an initial test concentration

of 10 µg/ml. For testing at 30µg/ml, working stock solutions of 12mg/ml were prepared.

Citrated dog blood containing the test compound (5 ml, 10 µg/ml) was placed into a plastic Petri dish lid, which was kept at 37°C on a heated pad. Parafilm was stretched over the open top to form a tight membrane for the fleas to feed through. The test chamber containing the fleas was placed carefully onto the parafilm membrane and the fleas commenced feeding.

The fleas were allowed to feed for 2 hours and the test chambers were then removed and stored overnight at room temperature.

The fleas were observed and the percentage of fleas killed recorded. Compounds were initially tested at 10µg/ml, wherefrom relevant dose responses (100, 30, 10, 3, 1, 0.3, 0.1µg/ml) were conducted and repeated n=5. Data was plotted to generate ED80, ED90 & ED95 values.

The compounds of the present invention have significantly better activity than the prior art compounds. All the examples of the present invention have flea ED80 values of less than 100µg/ml. Results for some of the compounds are presented below.

Example	Flea feed ED80 results
16	1
39	3
44	0.1

Instruments used to acquire characterising data

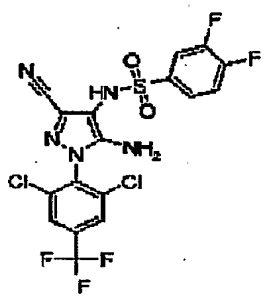
Nuclear magnetic resonance spectral data were obtained using Varian Inova 300, Varian Inova 400, Varian Mercury 400, Varian Unityplus 400, Bruker AC 300MHz, Bruker AM 250MHz or Varian T60 MHz spectrometers, the observed chemical shifts being consistent with the proposed structures. Mass spectral data were

obtained on a Waters Micromass ZQ, or a Hewlett Packard GCMS System Model 5971 spectrometer. The calculated and observed ions quoted refer to the isotopic composition of lowest mass. HPLC means high performance liquid chromatography. Room temperature means 20 to 25°C.

Compounds of the present invention are exemplified below.

Example 1

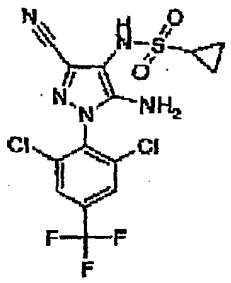
N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-3,4-difluorobenzenesulfonamide



To a solution of Preparation 1 (163 mg) in methanol (4 ml) was added hydrochloric acid (4M, 3 ml). The reaction mixture was then heated at 90°C for 12 h. The reaction mixture was concentrated *in vacuo* and to the residue was added water (15 ml). This solution was neutralised by addition of saturated aqueous sodium hydrogen carbonate and then extracted with dichloromethane (3 x 10 ml). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved in acetonitrile (7 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 21.2 mm Phenomenex LUNA 100Å C18 column) using an acetonitrile : water gradient [10 : 90 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 1 (255 mg).
^{1}H-NMR δ (CDCl3): 3.46 - 3.46 (2.0H), 6.28 - 6.31 (1.0H), 7.32 - 7.38 (1.0H), 7.56 - 7.61 (2.0H), 7.77 - 7.79 (2.0H)

Example 2

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}cyclopropanesulfonamide



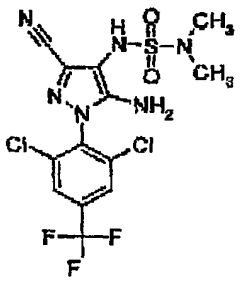
To a solution of Preparation 2 (200 mg, 0.40 mmol) in methanol (5 ml) was added hydrochloric acid (4M, 3 ml). The reaction mixture was then heated at reflux for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between dichloromethane (20 ml) and water (20 ml). The two layers were separated and the aqueous layer was extracted with ethyl acetate (20 ml). The combined organic layers were then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was pre-absorbed onto silica and purified using an Isolute™ column (silica, 20 g) with gradient elution, cyclohexane : ethyl acetate [2 : 1 to 1 : 1]. The appropriate fractions were combined and concentrated to give Example 2 (189 mg).

MS (ES): M/Z [MH+] 440.0; expected mass for C14H10Cl2F3N5O2S + H is 440.0

^{1}H-NMR δ (CD3OD): 0.97 - 1.06 (4.0H), 2.57 - 2.64 (1.0H), 7.97 - 8.00 (2.0H).

Example 3

N'-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N,N*-dimethylsulfamide



To a solution of crude Preparation 3 (200 mg), in methanol (4 ml) was added hydrochloric acid (4M, 3 ml). The reaction mixture was then heated at 90°C for 12 h. The reaction mixture was concentrated *in vacuo* and to the residue was added water (15 ml). This solution was neutralised by addition of saturated aqueous

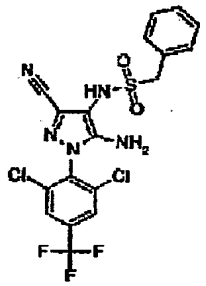
sodium hydrogen carbonate and then extracted with dichloromethane (3 x 10 ml). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved in acetonitrile (4 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 21.2 mm Phenomenex LUNA 100 Å C18 column) using an acetonitrile : water gradient [10 : 90 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 3 (50 mg).

MS (ES): M/Z [MH+] 443.2; expected mass for C13H11Cl2F3N6O2S + H is 443.0

^{1}H-NMR δ (CD3OD): 2.82 - 2.89 (6.0H), 7.96 - 8.01 (2.0H).

Example 4

N-[5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl]-1-phenylmethanesulfonamide



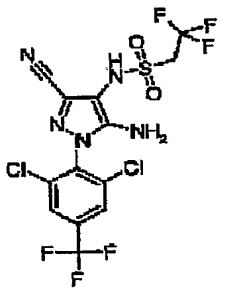
To a solution of Preparation 4 (145 mg) in methanol (4 ml) was added hydrochloric acid (4M, 3 ml). The reaction mixture was then heated at 90°C for 12 h. The reaction mixture was concentrated *in vacuo* and to the residue was added water (15 ml). This solution was neutralised by addition of saturated aqueous sodium hydrogen carbonate and then extracted with dichloromethane (3 x 10 ml). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved in acetonitrile (2 ml) and passed through a 0.45μm filter. The solution was purified by automated preparative liquid chromatography (Gilson system, 150 mm x 21.2 mm Phenomenex LUNA II C18 5μm column) using an acetonitrile : water gradient [60 : 40 to 98 : 2] . The appropriate fractions were concentrated *in vacuo* to give Example 4 (55 mg).

MS (ES): M/Z [MH+] 490.0; expected mass for C18H12Cl2F3N5O2S + H is 490.0

^{1}H-NMR δ (CD3OD): 4.41 - 4.44 (2.0H), 7.30 - 7.37 (3.0H), 7.41 - 7.46 (2.0H), 7.95 - 8.01 (2.0H).

Example 5

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-2,2,2-trifluoroethanesulfonamide



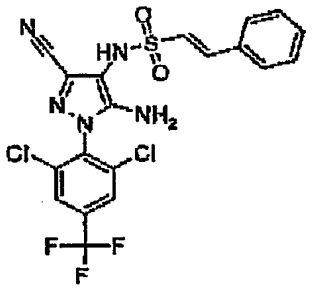
To a solution of Preparation 5 (200 mg), a mixture of mono and bis sulphonated product, in methanol (4 ml) was added hydrochloric acid (4M, 3 ml). The reaction mixture was then heated at 90°C for 12 h. The reaction mixture was concentrated *in vacuo* and to the residue was added water (15 ml). This solution was neutralised by addition of saturated aqueous sodium hydrogen carbonate and then extracted with dichloromethane (3 x 10 ml). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved in acetonitrile (3 ml) and passed through a 0.45µm filter. The solution was purified by automated preparative liquid chromatography (Gilson system, 150 mm x 21.2 mm Phenomenex LUNA II C18 5µm column) using an acetonitrile : water gradient [60 : 40 to 98 : 2] . The appropriate fractions were concentrated *in vacuo* to give Example 5 (56 mg).

MS (ES): M/Z [MH+] 482.0; expected mass for C13H7Cl2F6N5O2S + H is 482.0

^{1}H-NMR δ (CD3OD): 4.13 - 4.20 (2.0H), 7.97 - 8.01 (2.0H)

Example 6

(*E*)-*N*-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-2-phenylethylenesulfonamide



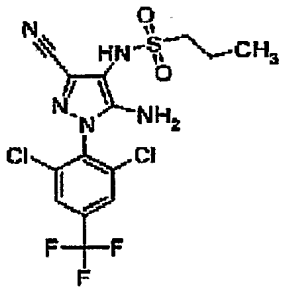
To a solution of Preparation 6 (155 mg) in methanol (4 ml) was added hydrochloric acid (4M, 3 ml). The reaction mixture was then heated at 90°C for 12 h. The reaction mixture was concentrated *in vacuo* and to the residue was added water (15 ml). This solution was neutralised by addition of saturated aqueous sodium hydrogen carbonate and then extracted with dichloromethane (3 x 10 ml). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved in acetonitrile (3 ml) and passed through a 0.45µm filter. The solution was purified by automated preparative liquid chromatography (Gilson system, 150 mm x 21.2 mm Phenomenex LUNA II C18 5µm column) using an acetonitrile : water gradient [60 : 40 to 98 : 2] . The appropriate fractions were concentrated *in vacuo* to give Example 6 (58 mg).

MS (ES): M/Z [MH+] 502.0; expected mass for C19H12Cl2F3N5O2S + H is 502.0

^{1}H-NMR δ (CD3OD): 6.97 - 7.03 (1.0H), 7.25 - 7.31 (1.0H), 7.35 - 7.40 (3.0H), 7.52 - 7.56 (2.0H), 7.90 - 7.95 (2.0H).

Example 7

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}propane-1-sulfonamide



To a solution of Preparation 7 (109 mg) in methanol (4 ml) was added hydrochloric acid (4M, 3 ml). The reaction mixture was then heated at 90°C for 12 h. The

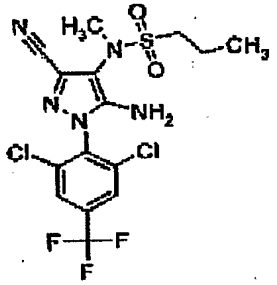
reaction mixture was concentrated *in vacuo* and to the residue was added water (15 ml). This solution was neutralised by addition of saturated aqueous sodium hydrogen carbonate and then extracted with dichloromethane (3 x 10 ml). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved in acetonitrile (1 ml) and water (1 drop) and passed through a 0.45µm filter. The solution was purified by automated preparative liquid chromatography (Gilson system, 150 mm x 21.2 mm Phenomenex LUNA II C18 5µm column) using an acetonitrile : water gradient [60 : 40 to 98 : 2] . The appropriate fractions were concentrated *in vacuo* to give Example 7 (57 mg).

MS (ES): M/Z [MH+] 442.0; expected mass for C14H12Cl2F3N5O2S + H is 442.0

^{1}H-NMR δ (CD3OD): 1.03 - 1.08 (3.0H), 1.87 - 1.95 (2.0H), 3.06 - 3.12 (2.0H), 7.96 - 8.01 (2.0H).

Example 8

N-(5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl)-*N*-methylpropane-1-sulfonamide



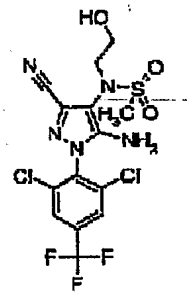
To a solution of Example 7 (38 mg, 0.086 mmol) in acetone (3 ml) was added methyl iodide (5 µl, 0.087 mmol) and potassium carbonate (20 mg). The reaction mixture was then stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (3 ml) and water (3 ml). The organic phase was then separated, dried and concentrated *in vacuo*. The crude product was dissolved in acetonitrile (1 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 21.2 mm Phenomenex LUNA 100Å C18 column) using an acetonitrile : water gradient [10 : 90 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 8 (31 mg).

MS (ES): M/Z [MH+] 456.0; expected mass for C15H14Cl2F3N5O2S + H is 456.0

^{1}H-NMR δ (CD3OD): 1.03 - 1.08 (3.0H), 1.84 - 1.92 (2.0H), 3.14 - 3.19 (2.0H), 3.27 - 3.28 (3.0H), 7.95 - 8.01 (2.0H).

Example 9

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(2-hydroxyethyl)methanesulfonamide



Precursors used to synthesise Example 9: Preparation 8

Reaction: Method 1

Workup: Method 1

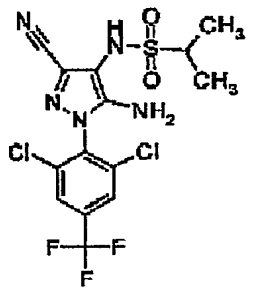
The crude product was dissolved in acetonitrile (3 ml) and dimethyl sulphoxide (1 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 21.2 mm Phenomenex LUNA 100 Å C18 column) using an acetonitrile : water gradient [10 : 90 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 9 (155 mg).

MS (ES): M/Z [MH+] 458.0; expected mass for C14H12Cl2F3N5O3S + H is 458.0

^{1}H-NMR δ (CD3OD): 3.07 - 3.08 (3.0H), 3.61 - 3.75 (4.0H), 7.98 - 8.01 (2.0H)

Example 10

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}propane-2-sulfonamide



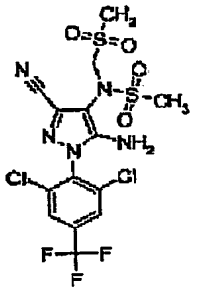
To a solution of Preparation 9 (186 mg, 0.31 mmol) in tetrahydrofuran (10 ml) and methanol (5 ml) was added hydrochloric acid (4M, 5 ml). The reaction mixture was then heated at reflux for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between water (20 ml) and dichloromethane (20 ml). The organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved in acetonitrile (1 ml) and water (1 drop) and the solution was passed through a filter (0.45 μm). The filtrate was purified by automated preparative liquid chromatography (Gilson system, 150 mm x 21.2 mm Phenomenex LUNA II C18 column) using an acetonitrile : water gradient [50 : 50 to 98 : 2]. The appropriate fractions were combined and concentrated *in vacuo* to give Example 10 (62 mg).

MS (ES): M/Z [MH+] 442.0; expected mass for C14H12Cl2F3N5O2S + H is 442.0

^{1}H-NMR δ (CD3OD): 1.40 - 1.44 (6.0H), 3.28 - 3.36 (1.0H), 7.95 - 8.00 (2.0H).

Example 11

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-[(methylsulfonyl)methyl]methanesulfonamide



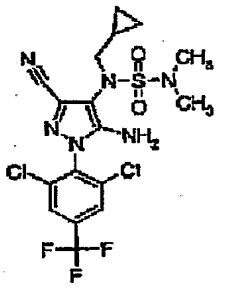
To a solution of Example 64 (108 mg, 0.23 mmol) in acetone (35 ml) was added sodium carbonate (318 mg, 3.04 mmol), followed by Oxone® (924 mg, 1.52 mmol) in water (12 ml). The reaction mixture was then stirred at room temperature for 5 hours. To the reaction mixture was added water and the solution was extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was dissolved in a mixture of acetonitrile (1 ml) and water (1 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA C18(2) 10μm column) using an acetonitrile : water gradient [45 : 55 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 11 (55 mg).

MS (ES): M/Z [MH+] 505.9; expected mass for C14H12Cl2F3N5O4S2 + H is 506.0

^{1}H-NMR δ (CDCl3): 3.05 - 3.07 (3.0H), 3.15 - 3.18 (3.0H), 4.43 - 4.5 (2.0H), 7.74 - 7.80 (2.0H).

Example 12

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(cyclopropylmethyl)-*N'*,*N'*-dimethylsulfamide



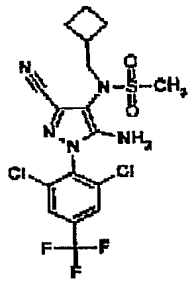
A suspension of Preparation 11 (96 mg, 0.17 mmol) in methanol (3 ml) and hydrochloric acid (2M, 3 ml) was heated at 60°C for 7 days. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between water (50 ml) and dichloromethane (50 ml). The two layers were separated and the aqueous layer was extracted with dichloromethane (2 x 25 ml). The combined organic phases were then dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. The crude product was dissolved in dimethyl sulphoxide (900 µl), acetonitrile (400 µl) and water (200 µl) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA C18(2) 10µm column) using an acetonitrile : water gradient [55 : 45 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 12 (39 mg).

MS (ES): M/Z [MH+] 496.9; expected mass for C17H17Cl2F3N6O2S + H is 497.1

^{1}H-NMR δ (DMSOd_6): 0.03 - 0.07 (2.0H), 0.39 - 0.43 (2.0H), 0.87 - 0.92 (1.0H), 2.73 - 2.76 (6.0H), 6.12 - 6.18 (2.0H), 8.20 - 8.23 (2.0H).

Example 13

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(cyclobutylmethyl)methanesulfonamide



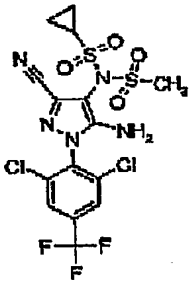
To a solution of Preparation 12 (102 mg, 0.19 mmol) in methanol (4 ml) was added hydrochloric acid (4N, 2 ml) and the reaction mixture was heated at reflux for 4 h. To the reaction mixture was added ethyl acetate and water. The two layers were separated and the aqueous layer was re-extracted with ethyl acetate (x 3). The combined organic layers were dried ($MgSO_4$) and concentrated under nitrogen. The crude product was dissolved in a mixture of acetonitrile, water and dimethyl sulphoxide (4 : 2 : 9, 1.5 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA C18(2) 10µm column) using an acetonitrile : water gradient [55 : 45 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 13 (41 mg).

MS (ES): M/Z [MH+] 481.9; expected mass for C17H16Cl2F3N5O2S + H is 482.0

^{1}H-NMR δ (CDCl3): 1.67 - 1.77 (2.0H), 1.81 - 1.92 (2.0H), 1.97 - 2.05 (2.0H), 2.41 - 2.49 (1.0H), 3.01 - 3.04 (3.0H), 3.64 - 3.73 (2.0H), 4.08 - 4.16 (2.0H), 7.74 - 7.79 (2.0H).

Example 14

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(methylsulfonyl)cyclopropanesulfonamide



A suspension of Preparation 13 (150 mg, 0.26 mmol) in methanol (3 ml) and hydrochloric acid (4M, 3 ml) was heated at 60°C for 2 days. To the reaction

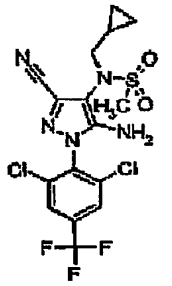
mixture was added 1,2-dichloroethane (4 ml) and the mixture was heated at 60°C for a further 4 days. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between water (25 ml) and dichloromethane (25 ml). The two layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 25 ml). The combined organic phases were then dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved in a mixture of acetonitrile, water and dimethyl sulphoxide (2 : 1 : 7, 2 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA C18(2) 10µm column) using an acetonitrile : water gradient [55 : 45 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 14 (3 mg).

MS (ES): M/Z [MH+] 517.9; expected mass for C15H12Cl2F3N5O4S2 + H is 518.0

^{1}H-NMR δ (CD3OD): 1.18 - 1.26 (4.0H), 3.06 - 3.10 (1.0H), 3.45 - 3.46 (3.0H), 7.55 - 7.59 (2.0H).

Example 15

N-[5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl]-*N*-(cyclopropylmethyl)methanesulfonamide



Precursors used to synthesise Example 15: Preparation 14

Reaction: Method 1

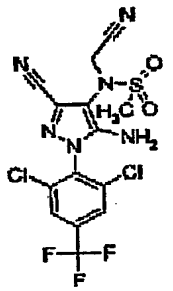
Workup: Method 1

The crude product was dissolved in acetonitrile (4 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 21.2 mm Phenomenex LUNA 100 Å C18 column) using an acetonitrile : water gradient [10 90 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give the Example 15.

MS (ES): M/Z [MH+] 468.3; expected mass for C16H14Cl2F3N5O2S + H is 468.0
^{1}H-NMR δ (CDCl3): 0.17 - 0.23 (2.0H), 0.50 - 0.56 (2.0H), 0.97 - 1.05 (1.0H), 3.06 - 3.07 (3.0H), 3.50 - 3.55 (2.0H), 4.15 - 4.19 (2.0H), 7.77 - 7.78 (2.0H).

Example 16

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(cyanomethyl)methanesulfonamide



Precursors used to synthesise Example 16: Preparation 15

Reaction: Method 1

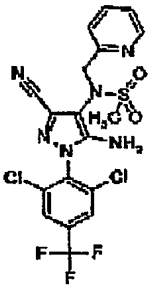
Workup: Method 1

The crude product was dissolved in acetonitrile (4 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 21.2 mm Phenomenex LUNA 100 Å C18 column) using an acetonitrile : water gradient [10 : 90 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give the Example 16.

MS (ES): M/Z [MH+] 453.2; expected mass for C14H9Cl2F3N6O2S + H is 453.0
^{1}H-NMR δ (CDCl3): 3.08 - 3.12 (3.0H), 3.30 - 3.39 (2.0H), 4.49 - 4.52 (2.0H), 7.69 - 7.72 (2.0H).

Example 17

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(pyridin-2-ylmethyl)methanesulfonamide



Precursors used to synthesise Example 17: Preparation 16

Reaction: Method 1

Workup: Method 1

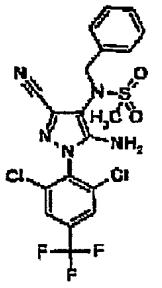
The crude product was dissolved in acetonitrile (4 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 21.2 mm Phenomenex LUNA 100 Å C18 column) using an acetonitrile : water gradient [10 : 90 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 17.

MS (ES): M/Z [MH+] 505.3; expected mass for C18H13Cl2F3N6O2S + H is 505.0

^{1}H-NMR δ (CDCl3): 3.06 - 3.08 (3.0H), 4.91 - 4.98 (2.0H), 7.23 - 7.28 (2.0H), 7.32 - 7.36 (1.0H), 7.71 - 7.73 (2.0H), 8.51 - 8.54 (1.0H).

Example 18

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-benzylmethanesulfonamide



Precursors used to synthesise Example 18: Preparation 17

Reaction: Method 1

Workup: Method 1

The crude product was dissolved in acetonitrile (4 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 21.2 mm

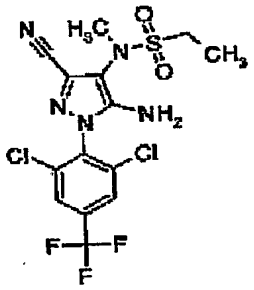
Phenomenex LUNA 100 Å C18 column) using an acetonitrile : water gradient [10 : 90 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 18.

MS (ES): M/Z [MH+] 504.3; expected mass for C19H14Cl2F3N5O2S + H is 504.0

^{1}H-NMR δ (CDCl3): 3.15 - 3.16 (3.0H), 3.66 - 3.71 (2.0H), 7.24 - 7.28 (3.0H), 7.29 - 7.33 (2.0H), 7.67 - 7.69 (2.0H).

Example 19

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-methylethanesulfonamide



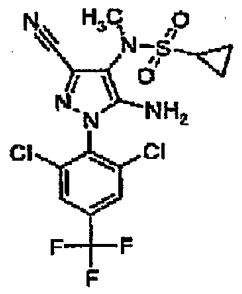
To a solution of Example 63 (28 mg, 65.4 µmol) in acetone (3 ml) was added methyl iodide (4 µl, 65.4 µmol) and potassium carbonate (9 mg, 65.4 µmol) and the reaction mixture was stirred for 18 h at room temperature. Further methyl iodide (3 µl, 4.8 µmol) was added and the reaction mixture was stirred for another 4 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between dichloromethane (5 ml) and water (5 ml). The organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved in a mixture of acetonitrile (0.5 ml) and dimethyl sulphoxide (0.3 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA II C18 10µm column) using an acetonitrile : water gradient [10 : 90 to 98 : 2] . The appropriate fractions were concentrated *in vacuo* to give Example 19 (18 mg).

MS (ES): M/Z [MH+] 442.3; expected mass for C14H12Cl2F3N5O2S + H is 442.0

^{1}H-NMR δ (CDCl3): 1.46 - 1.51 (3.0H), 3.15 - 3.22 (2.0H), 3.38 - 3.40 (2.0H), [4.15 - 4.27 (2.0H), 7.74 - 7.79 (2.0H).

Example 20

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-methylcyclopropanesulfonamide



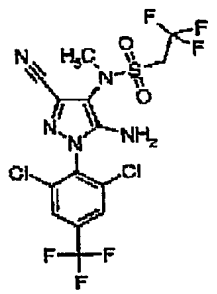
To a solution of Example 2 (50 mg, 0.11 mmol) in acetone (3 ml) was added methyl iodide (7.7 µl, 0.11 mmol) and potassium carbonate (15 mg). The reaction mixture was then stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (3 ml) and water (3 ml). The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved in a mixture of acetonitrile (0.5 ml) and dimethyl sulphoxide (0.3 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA II C18 10µm column) using an acetonitrile : water gradient [10 : 90 to 98 : 2] . The appropriate fractions were concentrated *in vacuo* to give Example 20 (30 mg).

MS (ES): M/Z [MH+] 453.9; expected mass for C15H12Cl2F3N5O2S + H is 454.0

^{1}H-NMR δ (CD3OD): 1.00 - 1.10 (4.0H), 2.64 - 2.70 (1.0H), 3.31 - 3.33 (3.0H), 7.96 - 8.01 (2.0H).

Example 21

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-methyl-2,2,2-trifluoroethanesulfonamide



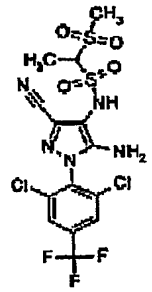
To a solution of Example 5 (42 mg, 0.087 mmol) in acetone (3 ml) was added methyl iodide (5 µl, 0.087 mmol) and potassium carbonate (20 mg). The reaction mixture was then stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (3 ml) and water (3 ml). The organic phase was then separated, dried and concentrated *in vacuo*. The crude product was dissolved in acetonitrile (1 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 21.2 mm Phenomenex LUNA 100Å C18 column) using an acetonitrile : water gradient [10 : 90 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 21 (29 mg).

MS (ES): M/Z [MH+] 495.9; expected mass for C14H9Cl2F6N5O2S + H is 496.0

^{1}H-NMR δ (CD3OD): 3.31 - 3.32 (3.0H), 4.17 - 4.34 (2.0H), 7.97 - 8.00 (2.0H).

Example 22

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-1-(methylsulfonyl)ethanesulfonamide



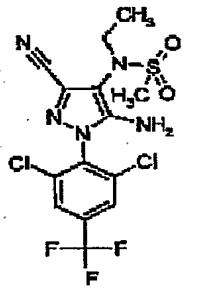
To a solution of Example 65 (90 mg, 0.18 mmol) in acetone (3 ml) was added methyl iodide (11 µl, 0.18 mmol) and potassium carbonate (20 mg). The reaction mixture was then stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (3

ml) and water (3 ml). The organic phase was then separated, dried and concentrated *in vacuo*. The crude product was dissolved in a mixture of acetonitrile (0.5 ml) and dimethyl sulphoxide (0.3 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA II C18 10µm column) using an acetonitrile : water gradient [10 : 90 to 98 : 2]. The appropriate fractions were concentrated *in vacuo* to give Example 22 (21 mg).

^{1}H-NMR δ (DMSOd_6): 1.55 - 1.60 (3.0H), 3.21 - 3.22 (3.0H), 5.20 - 5.26 (1.0H), 6.38 - 6.49 (2.0H), 8.22 - 8.24 (2.0H).

Example 23

N-(5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl)-*N*-ethylmethanesulfonamide



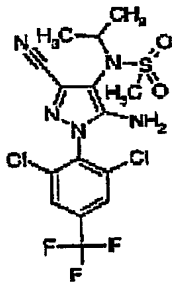
To a solution of Preparation 19, (150 mg, 0.32 mmol) in acetone (5 ml) was added potassium carbonate (71 mg, 0.51 mmol), followed by iodoethane (38 µl, 0.48 mmol). The reaction mixture was then heated at reflux for 2 h. The reaction mixture was concentrated under nitrogen and the residue partitioned between ethyl acetate and water. The two layers were separated and the aqueous layer was extracted with ethyl acetate (x 2). The combined organic phases were dried ($MgSO_4$) and concentrated under nitrogen to give the protected amine. To a solution of the protected amine in methanol was added hydrochloric acid (4N, 2 ml) and the reaction mixture was heated at reflux for 4 h. To the reaction mixture was added ethyl acetate and water. The two layers were separated and the aqueous layer was re-extracted with ethyl acetate (x 3). The combined organic layers were dried ($MgSO_4$) and concentrated under nitrogen. The crude product was dissolved in acetonitrile (3 ml), with sonication, and purified by automated

preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA C18(2) 10µm column) using an acetonitrile : water gradient [50 : 50 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 23 (50 mg).

MS (ES): M/Z [MH+] 442.3; expected mass for C14H12Cl2F3N5O2S + H is 442.0
^{1}H-NMR δ (DMSOd_6): 1.03 - 1.09 (3.0H), 2.98 - 3.04 (3.0H), 3.45 - 3.56 (2.0H), 6.35 - 6.43 (2.0H), 8.21 - 8.24 (2.0H).

Example 24

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-isopropylmethanesulfonamide



Precursors used to synthesise Example 24: Preparation 20

Reaction: Method 1

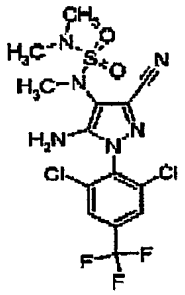
Workup: Method 1

The crude product was dissolved in acetonitrile (4 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 21.2 mm Phenomenex LUNA 100 Å C18 column) using an acetonitrile : water gradient [10 : 90 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 24 (163 mg).

MS (ES): M/Z [MH+] 456.3; expected mass for C15H14Cl2F3N5O2S + H is 456.0
^{1}H-NMR δ (CDCl3): 1.16 - 1.23 (3.0H), 1.29 - 1.35 (3.0H), 3.06 - 3.09 (3.0H), 4.11 - 4.16 (2.0H), 4.58 - 4.63 (1.0H), 7.76 - 7.79 (2.0H).

Example 25

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*,*N*',*N*'-trimethylsulfamide



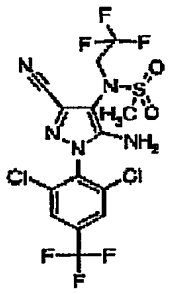
To a solution of Preparation 21 (90 mg) in methanol (5 ml) was added hydrochloric acid (4M, 3 ml) and the reaction mixture was heated at 60°C for 18 h. To the reaction mixture was added water (20 ml) and the resulting mixture was extracted with dichloromethane (20 ml), followed by ethyl acetate (20 ml). The combined organic extracts were then concentrated *in vacuo* to give Example 25.

MS (ES): M/Z [MH+] 457.3; expected mass for C14H13Cl2F3N6O2S + H is 457.0

^{1}H-NMR δ (CDCl3): 2.88 - 2.95 (6.0H), 3.30 - 3.35 (3.0H), 4.25 - 4.34 (2.0H), 7.74 - 7.80 (2.0H).

Example 26

N-(5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(2,2,2-trifluoroethyl)methanesulfonamide



To a solution of Preparation 19 (250 mg, 0.53 mmol) in 1-methyl-2-pyrrolidinone (anhydrous, 5 ml) was added sodium hydride (60% in oil, 16.6 mg, 0.69 mmol) and 2,2,2-trifluoroethyl trichloromethanesulphonate (195 mg, 0.69 mmol). The reaction mixture was then stirred at room temperature for 3 h. To the reaction mixture was added dichloromethane (20 ml) and the resulting mixture was extracted with water (20 ml). The organic phase was washed with water (2 x 20 ml) and brine (2 x 20 ml), dried (Na_2SO_4) and concentrated *in vacuo*. To the residue was added methanol (5 ml) and hydrochloric acid (4M, 3 ml) and the mixture was heated at

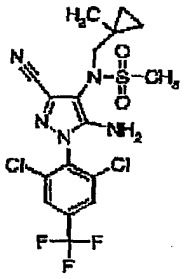
reflux for 60 h. The reaction mixture was concentrated *in vacuo* and to the residue was added ethyl acetate (20 ml) and water (20 ml). The organic phase was separated, washed with water (2 x 20 ml) and brine (2 x 20 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved in acetonitrile/dimethyl sulphoxide/water (1 : 4 : 1, 6 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA C18(2) 10μm column) using an acetonitrile : water gradient [52.5 : 47.5 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 26 (135 mg).

MS (ES): M/Z [MH+] 496.2; expected mass for C14H9Cl2F6N5O2S + H is 496.0

^{1}H-NMR δ (CDCl3): 3.10 - 3.14 (3.0H), 4.07 - 4.33 (4.0H), 7.74 - 7.80 (2.0H).

Example 27

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-[(1-methylcyclopropyl)methyl]methanesulfonamide



To a solution of Preparation 22 (149 mg, 0.28 mmol) in methanol (5 ml) was added hydrochloric acid (2N, 2.5 ml) and the reaction mixture was heated at reflux for 18 h. The mixture was concentrated *in vacuo* and the residue was partitioned between aqueous sodium hydrogen carbonate solution (10 ml) and ethyl acetate (10 ml). The organic phase was then separated, dried ($MgSO_4$) and concentrated *in vacuo*.

To the residue was added methanol (4 ml) and hydrogen chloride in dioxane (4M, 1.5 ml) and the reaction mixture was heated at 80°C for 4 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between saturated aqueous sodium hydrogen carbonate solution (6 ml) and ethyl acetate (6 ml). The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was dissolved in acetonitrile/water (7 : 3, 3.2 ml) and purified by

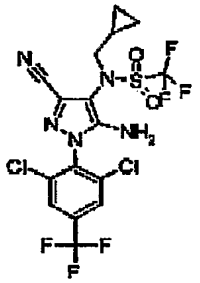
automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA C18(2) 10µm column) using an acetonitrile : water gradient [55 : 45 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 27 (57 mg).

MS (ES): M/Z [MH+] 482.3; expected mass for C17H16Cl2F3N5O2S + H is 482.0

^{1}H-NMR δ (CD3OD): 0.25 - 0.29 (4.0H), 1.19 - 1.22 (3.0H), 2.99 - 3.01 (3.0H), 7.99 - 8.01 (2.0H).

Example 28

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(cyclopropylmethyl)-1,1,1-trifluoromethanesulfonamide



To a solution of Preparation 23 (250 mg, 0.48 mmol) in acetone (6 ml) was added potassium carbonate (100 mg, 0.72 mmol), a catalytic amount of sodium iodide and (bromomethyl)cyclopropane (69.5 µl, 0.72 mmol). The reaction mixture was then stirred at 60°C for 18 h. The reaction mixture was concentrated under a stream of nitrogen and the residue was partitioned between dichloromethane (20 ml) and water (20 ml). The two layers were separated and the organic phase was washed with water, dried (Na_2SO_4) and concentrated *in vacuo* to give the protected compound. To a solution of the protected compound in methanol (5 ml) was added hydrochloric acid (4M, 3 ml) and the reaction mixture was heated at reflux The reaction mixture was concentrated *in vacuo* and the residue was extracted with ethyl acetate (20 ml). The organic phase was washed with water (2 x 20 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved in a mixture of acetonitrile (1 ml), dimethyl sulphoxide (2.4 ml) and water (0.6 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA C18(2) 10µm column) using an

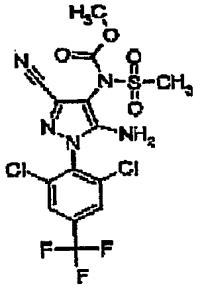
acetonitrile : water gradient [60 : 40 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 28 (120 mg).

MS (ES): M/Z [MH+] 522.3; expected mass for C16H11Cl2F6N5O2S + H is 522.0

^{1}H-NMR δ (CDCl3): 0.19 - 0.29 (2.0H), 0.54 - 0.64 (2.0H), 0.99 - 1.10 (1.0H), 3.53 - 3.78 (2.0H), 4.01 - 4.13 (2.0H), 7.72 - 7.84 (2.0H).

Example 29

Methyl 5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl(methylsulfonyl)carbamate



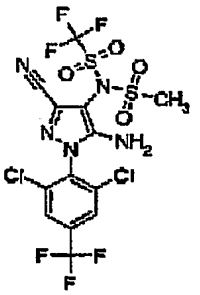
To a solution of Example 60 (100 mg, 0.24 mmol) in acetone (4 ml) was added potassium carbonate (50 mg, 0.36 mmol) and methyl chloroformate (22.4 µl, 0.29 mmol). The reaction mixture was then heated at reflux for 3 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between dichloromethane and water. The two layers were separated and the aqueous layer was extracted with dichloromethane (x 3). The combined organic layers were then dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was dissolved in acetonitrile/water (4 : 1, 5 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA C18(2) 10µm column) using an acetonitrile : water gradient [50 : 50 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 29 (90 mg).

MS (ES): M/Z [MH+] 471.8; expected mass for C14H10Cl2F3N5O4S + H is 472.0

^{1}H-NMR δ (CD3OD): 3.50 - 3.52 (3.0H), 3.85 - 3.86 (3.0H), 7.96 - 8.00 (2.0H).

Example 30

N-[5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl]-*N*-(methylsulfonyl)-1,1,1-trifluoromethanesulfonamide

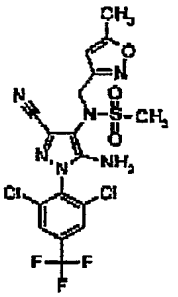


To a solution of Example 60 (73 mg, 0.18 mmol) in dichloromethane (4 ml), at 0°C, was added dropwise triethylamine (30 µl, 0.21 mmol), followed by trifluoromethanesulphonic anhydride (30 µl, 0.18 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 4 h. To the reaction mixture was added water and dichloromethane. The two layers were separated and the aqueous layer was extracted with dichloromethane (x 3). The combined organic phases were then dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was dissolved in acetonitrile/water (7 : 3, 5 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA C18(2) 10µm column) using an acetonitrile : water gradient [55 : 45 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 30 (50 mg).

^{1}H-NMR δ (CDCl3): 3.57 - 3.58 (3.0H), 4.12 - 4.20 (2.0H), 7.77 - 7.81 (2.0H).

Example 31

N-[5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl]-*N*-[(5-methylisoxazol-3-yl)methyl]methanesulfonamide



Precursors used to synthesise Example 31: Preparation 24

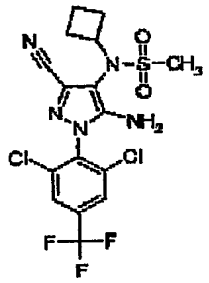
Reaction: Method 1

Workup: Method 1

The crude product was dissolved in a mixture of acetonitrile (1.2 ml), water (0.3 ml) and dimethyl sulphoxide (1.5 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA C18(2) 10μm column) using an acetonitrile : water gradient [55 : 45 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 31 (171 mg).
MS (ES): M/Z [MH+] 508.9; expected mass for C17H13Cl2F3N6O3S + H is 509.0
^{1}H-NMR δ (CDCl3): 2.36 - 2.38 (3.0H), 3.12 - 3.14 (3.0H), 4.36 - 4.54 (2.0H), 4.81 - 4.88 (2.0H), 6.00 - 6.03 (1.0H), 7.71 - 7.76 (2.0H).

Example 32

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-cyclobutylmethanesulfonamide

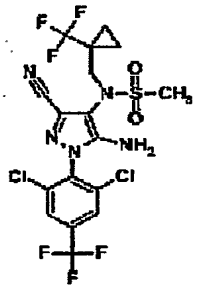


To a solution of Preparation 19 (200 mg, 0.43 mmol) in acetone (6 ml) was added potassium carbonate (177 mg, 1.29 mmol), followed by cyclobutyl bromide (173 mg, 1.29 mmol). The reaction mixture was then heated at reflux for 3 days. The reaction mixture was concentrated under nitrogen and the residue partitioned between ethyl acetate and water. The two layers were separated and the aqueous layer was extracted with ethyl acetate (x 2). The combined organic phases were dried ($MgSO_4$) and concentrated under nitrogen to give the protected product. To a solution of the protected amine in methanol (4 ml) was added hydrochloric acid (4N, 2 ml) and the reaction mixture was heated at reflux for 4 h. To the reaction mixture was added ethyl acetate and water. The two layers were separated and the aqueous layer was re-extracted with ethyl acetate (x 3). The combined organic layers were dried ($MgSO_4$) and concentrated under nitrogen. The crude product was dissolved in a mixture of acetonitrile, water and dimethyl sulphoxide (2 : 1 : 7, 4 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA C18(2)

10μm column) using an acetonitrile : water gradient [55 : 45 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 32 (78 mg).
MS (ES): M/Z [MH+] 467.9; expected mass for C16H14Cl2F3N5O2S + H is 468.0
^{1}H-NMR δ (CDCl3): 1.59 - 1.64 (2.0H), 1.91 - 2.03 (2.0H), 2.21 - 2.32 (2.0H), 3.03 - 3.05 (3.0H), 4.05 - 4.21 (2.0H), 4.61 - 4.70 (1.0H), 7.76 - 7.80 (2.0H).

Example 33

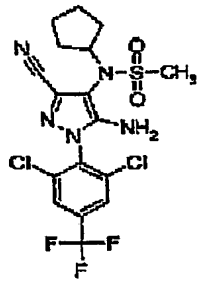
N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-{[1-(trifluoromethyl)cyclopropyl]methyl}methanesulfonamide



To a solution of Preparation 25 (150 mg, 0.25 mmol) in methanol (4 ml) was added hydrochloric acid (4N, 2 ml) and the reaction mixture was heated at reflux for 4 h. To the reaction mixture was added ethyl acetate and water. The two layers were separated and the aqueous layer was re-extracted with ethyl acetate (x 3). The combined organic layers were dried ($MgSO_4$) and concentrated under nitrogen. The crude product was dissolved in a mixture of acetonitrile, water and dimethyl sulphoxide (2 : 1 : 7, 2 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA C18(2) 10μm column) using an acetonitrile : water gradient [55 : 45 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 33 (98 mg).
MS (ES): M/Z [MH+] 535.9; expected mass for C17H13Cl2F6N5O2S + H is 536.0
^{1}H-NMR δ (DMSOd_6): 0.71 - 0.83 (2.0H), 0.91 - 1.00 (2.0H), 2.94 - 2.98 (3.0H), 3.43 - 3.51 (1.0H), 3.98 - 4.06 (1.0H), 6.34 - 6.46 (2.0H), 8.19 - 8.28 (2.0).

Example 34

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-cyclopentylmethanesulfonamide



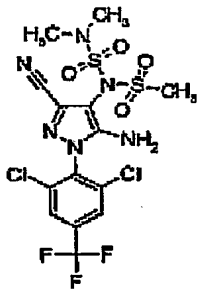
To a solution of Preparation 19 (100 mg, 0.21 mmol) in acetone (4 ml) was added potassium carbonate (47 mg, 0.34 mmol), followed by iodocyclopentane (37 µl, 0.32 mmol). The reaction mixture was then heated at reflux for 2 h. The reaction mixture was concentrated under nitrogen and the residue partitioned between ethyl acetate and water. The two layers were separated and the aqueous layer was extracted with ethyl acetate (x 2). The combined organic phases were dried ($MgSO_4$) and concentrated under nitrogen to give the protected product. To a solution of the protected amine in methanol (4 ml) was added hydrochloric acid (4N, 2 ml) and the reaction mixture was heated at reflux for 4 h. To the reaction mixture was added ethyl acetate and water. The two layers were separated and the aqueous layer was re-extracted with ethyl acetate (x 3). The combined organic layers were dried ($MgSO_4$) and concentrated under nitrogen. The crude product was dissolved in a mixture of acetonitrile, water and dimethyl sulphoxide (2 : 1 : 7, 2 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA C18(2) 10µm column) using an acetonitrile : water gradient [55 : 45 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 34 (38 mg).

MS (ES): M/Z [MH+] 481.9; expected mass for C17H16Cl2F3N5O2S + H is 482.0

^{1}H-NMR δ (DMSOd_6): 1.24 - 1.33 (1.0H), 1.41 - 1.55 (5.0H), 1.88 - 1.96 (2.0H), 3.01 - 3.04 (3.0H), 4.29 - 4.37 (1.0H), 8.18 - 8.24 (2.0H).

Example 35

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-[(dimethylamino)sulfonyl]methanesulfonamide



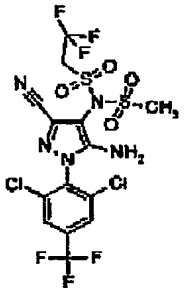
A suspension of Preparation 26 (150 mg, 0.26 mmol) in methanol (3 ml) and hydrochloric acid (4M, 3 ml) was heated at 60°C for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between water (25 ml) and dichloromethane (25 ml). The two layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 25 ml). The combined organic phases were then dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved in a mixture of acetonitrile, water and dimethyl sulphoxide (2 : 1 : 7, 4 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA C18(2) 10µm column) using an acetonitrile : water gradient [55 : 45 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 35 (96 mg).

MS (ES): M/Z [MH+] 520.9; expected mass for C14H13Cl2F3N6O4S2 + H is 521.0

^{1}H-NMR δ (CDCl3): 2.98 - 3.02 (6.0H), 3.44 - 3.47 (3.0H), 4.25 - 4.33 (2.0H), 7.76 - 7.80 (2.0H).

Example 36

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(methylsulfonyl)-2,2,2-trifluoroethanesulfonamide



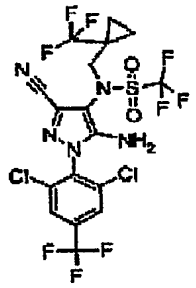
A suspension of Preparation 27 (70 mg, 0.11 mmol) in methanol (10 ml) and hydrochloric acid (4M, 5 ml) was heated at 80°C for 4 days. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between water (20 ml) and dichloromethane (40 ml). The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved in a mixture of acetonitrile, water and dimethyl sulphoxide (2 : 1 : 7, 4 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA C18(2) 10µm column) using an acetonitrile : water gradient [55 : 45 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 36 (46 mg).

MS (ES): M/Z [MH+] 559.8; expected mass for C14H9Cl2F6N5O4S2 + H is 560.0

^{1}H-NMR δ (CDCl3): 3.45 - 3.47 (3.0H), 4.11 - 4.15 (2.0H), 4.33 - 4.37 (1.0H), 4.55 - 4.59 (1.0H), 7.77 - 7.79 (2.0H).

Example 37

N-(5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-{[1-(trifluoromethyl)cyclopropyl]methyl}-1,1,1-trifluoromethanesulfonamide



To a solution of Preparation 28 (200 mg, 0.31 mmol) in methanol (5 ml) was added hydrochloric acid (2M, 3 ml) and the reaction mixture was heated at 80°C for 18 h. The reaction mixture was concentrated *in vacuo* and to the residue was added ethyl acetate (20 ml) and water (20 ml). The organic phase was separated, washed with water (2 x 20 ml) and brine (2 x 20 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved in a mixture of acetonitrile, dimethyl sulphoxide and water (2 : 1 : 7, 2 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA C18(2) 10µm column) using an acetonitrile : water gradient

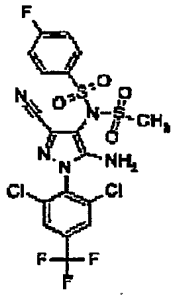
[60 : 40 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 37 (35 mg).

MS (ES): M/Z [MH+] 589.9; expected mass for C17H10Cl2F9N5O2S + H is 590.0

^{1}H-NMR δ (CDCl3): 0.59 - 0.63 (1.0H), 0.76 - 0.80 (1.0H), 1.05 - 1.09 (2.0H), 3.43 - 3.47 (1.0H), 4.11 - 4.16 (2.0H), 4.64 - 4.68 (1.0H), 7.77 - 7.80 (2.0H),

Example 38

N-(5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl)-*N*-(methylsulfonyl)-4-fluorobenzenesulfonamide



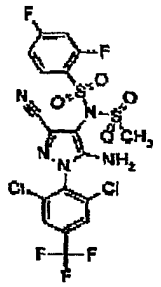
To a mixture of Example 60 (200 mg, 0.48 mmol), 4-dimethylaminopyridine (20 mg) and pyridine (0.2 ml) in dichloromethane (4 ml) was added 4-fluorobenzenesulphonyl chloride (93 mg, 0.48 mmol). The reaction mixture was then stirred for 18 h at room temperature. The reaction mixture was partitioned between ethyl acetate (25 ml) and water (25 ml) and the two layers were separated. The organic layer was then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified using an Isolute™ cartridge (silica, 25 g) with gradient elution, ethyl acetate : cyclohexane [15 : 85 to 1 : 1]. The appropriate fractions were combined and concentrated to give Example 38 (55 mg).

MS (ES): M/Z [MH+] 571.8; expected mass for C18H11Cl2F4N5O4S2 + H is 572.0

^{1}H-NMR δ (DMSOd_6): 3.69 - 3.75 (3.0H), 6.63 - 6.70 (2.0H), 7.51 - 7.57 (2.0H), 7.89 - 7.95 (2.0H), 8.19 - 8.29 (2.0H).

Example 39

N-(5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl)-*N*-(methylsulfonyl)-2,4-difluorobenzenesulfonamide



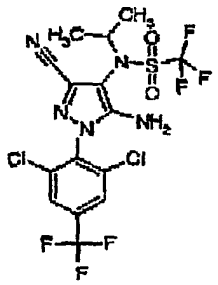
To a mixture of Example 60 (200 mg, 0.48 mmol), 4-dimethylaminopyridine (20 mg) and pyridine (0.2 ml) in dichloromethane (4 ml) was added 2,4-difluorobenzenesulphonyl chloride (102 mg, 0.48 mmol). The reaction mixture was then stirred for 18 h at room temperature. The reaction mixture was partitioned between ethyl acetate (25 ml) and water (25 ml) and the two layers were separated. The organic layer was then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified using an Isolute™ cartridge (silica, 25 g) with gradient elution, ethyl acetate : cyclohexane [15 : 85 to 1 : 1]. The appropriate fractions were combined and concentrated to give Example 39 (50 mg).

MS (ES): M/Z [MH+] 589.9; expected mass for C18H10Cl2F5N5O4S2 + H is 590.0

^{1}H-NMR δ (CDCl3): 3.58 - 3.60 (3.0H), 4.26 - 4.34 (2.0H), 7.00 - 7.10 (2.0H), 7.75 - 7.82 (2.0H), 7.92 - 8.01 (1.0H).

Example 40

N-[5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl]-*N*-isopropyl-1,1,1-trifluoromethanesulfonamide



To a solution of Preparation 29 (40 mg, 0.070 mmol) in tetrahydrofuran (4 ml) was added hydrochloric acid (4M, 3 ml). The reaction mixture was then heated at 80°C for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was

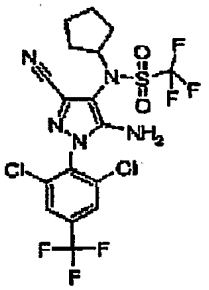
partitioned between water (25 ml) and dichloromethane (25 ml). The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved in a mixture of acetonitrile, water and dimethyl sulphoxide (4 : 1 : 5, 2 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA C18(2) 10µm column) using an acetonitrile : water gradient [60 : 40 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 40 (25 mg).

MS (ES): M/Z [MH+] 510.0; expected mass for C15H11Cl2F6N5O2S + H is 510.0

^{1}H-NMR δ (CDCl3): 1.22 - 1.27 (3.0H), 1.39 - 1.44 (3.0H), 3.92 - 4.03 (2.0H), 4.57 - 4.66 (1.0H), 7.74 - 7.82 (2.0H).

Example 41

N-[5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl]-*N*-cyclopentyl-1,1,1-trifluoromethanesulfonamide



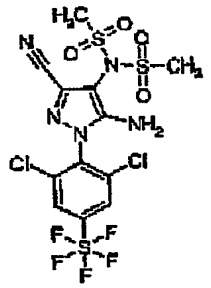
To a solution of Preparation 30 (63 mg, 0.11 mmol) in tetrahydrofuran (3 ml) was added hydrochloric acid (4M, 3 ml). The reaction mixture was then heated at 80°C for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between water (25 ml) and dichloromethane (25 ml). The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved in a mixture of acetonitrile, water and dimethyl sulphoxide (4 : 1 : 5, 2 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA C18(2) 10µm column) using an acetonitrile : water gradient [60 : 40 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 41 (12 mg).

MS (ES): M/Z [MH+] 536.0; expected mass for C17H13Cl2F6N5O2S + H is 536.0

^{1}H-NMR δ (CDCl3): 1.41 - 1.47 (1.0H), 1.54 - 1.64 (3.0H), 1.64 - 1.76 (2.0H), 1.95 - 2.04 (1.0H), 2.12 - 2.21 (1.0H), 3.92 - 4.03 (2.0H), 4.53 - 4.61 (1.0H), 7.71 - 7.84 (2.0H).

Example 42

N-{5-amino-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1*H*-pyrazol-4-yl}-*N*-(methylsulfonyl)methanesulfonamide



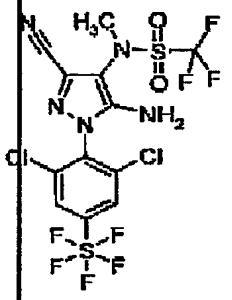
To a solution of Preparation 31 (200 mg, 0.45 mmol) in anhydrous dichloromethane (5 ml), at 0°C, was added triethylamine (124 µl, 0.9 mmol) and methanesulphonyl chloride (70 µl, 0.9 mol). The reaction mixture was then stirred under nitrogen for 30 min. To the reaction mixture was added dichloromethane (20 ml) and the resulting mixture was extracted with water (20 ml). The organic phase was washed with water (2 x 20 ml) and brine (2 x 20 ml), dried (Na_2SO_4) and concentrated *in vacuo*. To the residue was added methanol (5 ml) and hydrochloric acid (4M, 3 ml) and the mixture was heated at reflux for 60 h. The reaction mixture was concentrated *in vacuo* and to the residue was added ethyl acetate (20 ml) and water (20 ml). The organic phase was separated, washed with water (2 x 20 ml) and brine (2 x 20 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved in a mixture of acetonitrile and water (1 : 1 : 5 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA C18(2) 10µm column) using an acetonitrile : water gradient [60 : 40 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 42 (80 mg).

MS (ES): M/Z [MH+] 549.9; expected mass for C12H10Cl2F5N5O4S3 + H is 549.9

^{1}H-NMR δ (CDCl3): 3.41 - 3.47 (6.0H), 4.09 - 4.19 (2.0H), 7.88 - 7.94 (2.0H).

Example 43

N-{5-amino-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1*H*-pyrazol-4-yl}-*N*-methyl-1,1,1-trifluoromethanesulfonamide



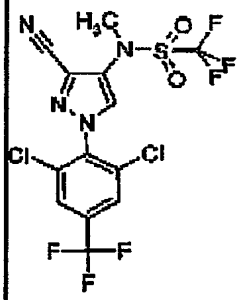
To Preparation 32 in methanol (5 ml) was added hydrochloric acid (4N, 3 ml) and the reaction mixture was heated at 80°C for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (20 ml) and water (20 ml). The organic layer was separated, washed with water (2 x 20 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved in a mixture of acetonitrile, dimethyl sulphoxide and water (4 : 5 : 1, 2 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA C18(2) 10µm column) using an acetonitrile : water gradient [60 : 40 to 95 : 5] The appropriate fractions were concentrated *in vacuo* to give Example 43 (60 mg).

MS (ES): M/Z [MH+] 539.9; expected mass for C12H7Cl2F8N5O2S2 + H is 539.9

^{1}H-NMR δ (CDCl3): 3.53 - 3.55 (3.0H), 4.08 - 4.12 (2.0H), 7.89 - 7.92 (2.0H).

Example 44

N-{3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-methyl-1,1,1-trifluoromethanesulfonamide



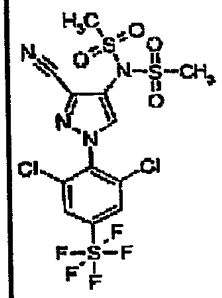
To a solution of Example 62 (150 mg, 0.31 mmol) in tetrahydrofuran (5 ml) was added dropwise *tert*-butyl nitrite (111 µl, 0.93 mmol). The reaction mixture was then heated at 60°C for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (20 ml) and water (20 ml). The organic layer was separated, washed with brine (20 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (silica, 10 g) eluting with dichloromethane/ethyl acetate [9 : 1]. The appropriate fractions were combined and concentrated to give the crude product. The crude product was dissolved in a mixture of acetonitrile, dimethyl sulphoxide and water (4 : 5 : 1, 2 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA C18(2) 10µm column) using an acetonitrile : water gradient [60 : 40 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 44 (80 mg).

MS (ES): M/Z [MH+] 467.0; expected mass for C13H6Cl2F6N4O2S + H is 467.0

^{1}H-NMR δ (CDCl3): 3.65 - 3.65 (3.0H), 7.77 - 7.80 (2.0H), 7.80 - 7.82 (1.0H).

Example 45

N-[3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1*H*-pyrazol-4-yl]-*N*-(methylsulfonyl)methanesulfonamide

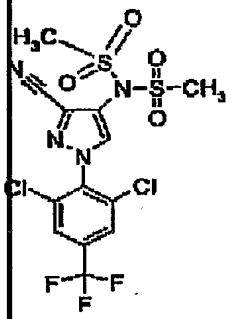


To a solution of Example 42 (310 mg, 0.56 mmol) in tetrahydrofuran (4 ml) was added dropwise *tert*-butyl nitrite (200 µl, 1.69 mmol). The reaction mixture was then heated at reflux for 16 h. The reaction mixture was concentrated *in vacuo* and the crude product was dissolved in acetonitrile (6 ml). The solution was passed through a 0.45 µm filter and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA II 10µm

C18 column) using an acetonitrile : water gradient [60 : 40 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 45 (169 mg).
^{1}H-NMR δ (Acetoned_6): 3.56 - 3.57 (6.0H), 8.28 - 8.35 (2.0H), 8.73 - 8.79 (1.0H).

Example 46

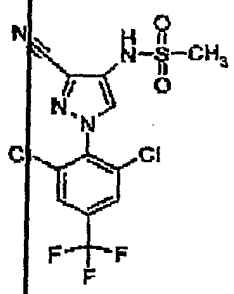
N-{3-cyano-1-[2,6-dichloro-4-trifluoromethylphenyl]-1*H*-pyrazol-4-yl}-*N*-(methylsulfonyl)methanesulfonamide



To a solution of Example 59 (1.0 g, 2.03 mmol) in tetrahydrofuran (100 ml) was added *tert*-butyl nitrite (0.72 ml, 6.1 mmol) and the reaction mixture was heated at 60°C for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was purified using an Isolute™ cartridge (silica, 50 g) with gradient elution, cyclohexane : ethyl acetate [1 : 0 to 3 : 2]. The appropriate fractions were combined and concentrated to give Example 46 (855 mg).
MS (ES): M/Z [MH+] 477.0; expected mass for C13H9Cl2F3N4O4S2 + H is 476.9
^{1}H-NMR δ (CDCl3): 3.45 - 3.46 (6.0H), 7.75 - 7.78 (2.0H), 7.80 - 7.83 (1.0H).

Example 47

N-{3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}methanesulfonamide



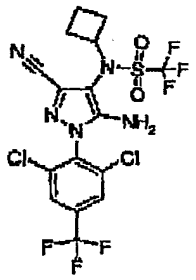
To a solution of Example 46 (855 mg, 1.79 mmol) in tetrahydrofuran (20 ml) was added potassium carbonate (617 mg, 4.48 mmol) in methanol (20 ml), containing a few drops of water. The reaction mixture was then stirred at room temperature for 2 h. The reaction mixture was concentrated *in vacuo* and to the residue was added hydrochloric acid (2M, 50 ml) and dichloromethane (100 ml). The organic phase was then separated, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified using an Isolute™ cartridge (silica, 20 g) with gradient elution, cyclohexane : ethyl acetate [1 : 0 to 1 : 1]. The appropriate fractions were combined and concentrated to give Example 47 (600 mg).

MS (ES): M/Z [MH+] 399.0; expected mass for C12H7Cl2F3N4O2S + H is 399.0

^{1}H-NMR δ (CDCl3): 3.08 - 3.10 (3.0H), 6.69 - 6.74 (1.0H), 7.73 - 7.78 (2.0H), 7.80 - 7.84 (1.0H).

Example 48

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-cyclobutyl-1,1,1-trifluoromethanesulfonamide



To a solution of Preparation 34 (250 mg, 0.43 mmol) in tetrahydrofuran (15 ml) was added hydrochloric acid (4M, 15 ml). The reaction mixture was then heated at reflux for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between water (50 ml) and dichloromethane (75 ml). The organic

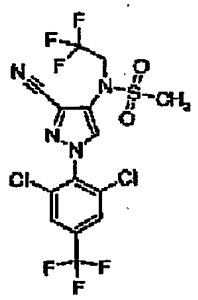
layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved in acetonitrile (6 ml) and the solution was passed through a 0.45 μm filter. The solution was then purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA II 10μm C18 column) using an acetonitrile : water gradient [60 : 40 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 48 (113 mg).

MS (ES): M/Z [MH+] 522.0; expected mass for C16H11Cl2F6N5O2S + H is 522.0

^{1}H-NMR δ (Acetoned_6): 0.23 - 0.31 (2.0H), 0.56 - 0.64 (2.0H), 1.12 - 1.20 (1.0H), 3.56 - 3.78 (2.0H), 6.12 - 6.22 (2.0H), 8.02 - 8.13 (2.0H).

Example 49

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(2,2,2-trifluoroethyl)methanesulfonamide

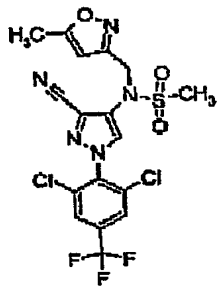


To a solution of sodium hydride (60% in oil, 14 mg, 0.35 mmol) in 1-methyl-2-pyrrolidinone (6 ml) was added Example 47 (115 mg, 0.29 mmol), followed by 2,2,2-trifluoroethyltrichloromethane sulphonate (185 mg, 0.66 mmol), added via syringe. The reaction mixture was then heated at 65°C for 6 days. The reaction mixture was concentrated *in vacuo* and the residue was purified using an Isolute™ cartridge (silica, 5 g) with gradient elution, dichloromethane : methanol [1 : 0 to 95 : 5]. The appropriate fractions were combined and concentrated to give Example 49 (41 mg).

^{1}H-NMR δ (CDCl3): 3.09 - 3.13 (3.0H), 4.27 - 4.34 (2.0H), 7.72 - 7.79 (2.0H), 7.83 - 7.87 (1.0H).

Example 50

N-{3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-[(5-methylisoxazol-3-yl)methyl]methanesulfonamide



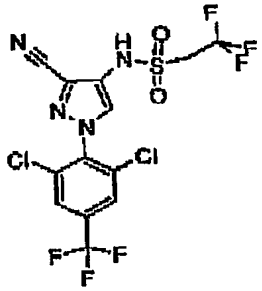
To a solution of Example 31 (75 mg, 0.15 mmol) in tetrahydrofuran (5 ml) was added dropwise *tert*-butyl nitrite (0.10 ml, 0.84 mmol). The reaction mixture was then heated at reflux for 18 h. The reaction mixture was concentrated *in vacuo* and the crude product was dissolved in acetonitrile/water (13 : 5, 1.8 ml). The solution was purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA II 10µm C18 column) using an acetonitrile : water gradient [55 : 45 to 95 : 5]. The appropriate fractions were concentrated *in vacuo* to give Example 50 (20 mg).

MS (ES): M/Z [MH+] 494.0; expected mass for C17H12Cl2F3N5O3S + H is 494.0

^{1}H-NMR δ (Acetoned_6): 2.36 - 2.38 (3.0H), 3.20 - 3.21 (3.0H), 4.91 - 4.93 (2.0H), 6.20 - 6.23 (1.0H), [8.05 - 8.11 (2.0H), 8.44 - 8.48 (1.0H).

Example 51

N-{3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-2,2,2-trifluoroethanesulfonamide



To a solution of Example 5 (195 mg, 0.40 mmol) in tetrahydrofuran (3 ml) was added dropwise *tert*-butyl nitrite (143 µl, 2.02 mmol). The reaction mixture was

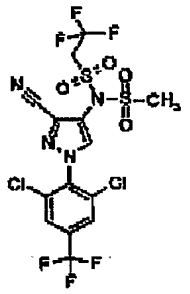
then heated at reflux for 2h. The reaction mixture was concentrated *in vacuo* and the crude product was dissolved in acetonitrile/water (1 : 1, 1.5 ml). The solution was purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA II 10µm C18 column) using an acetonitrile : 0.1% trifluoroacetic acid in water gradient [50 : 50 to 95 : 5]. The appropriate fractions were concentrated *in vacuo* to give Example 51 (18 mg).

MS (ES): M/Z [MH+] 467.0; expected mass for C13H6Cl2F6N4O2S + H is 467.0

^{1}H-NMR δ (Acetoned_6): 4.43 - 4.49 (2.0H), 8.08 - 8.11 (2.0H), 8.41 - 8.43 (1.0H).

Example 52

N-{3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(methylsulfonyl)-2,2,2-trifluoroethanesulfonamide

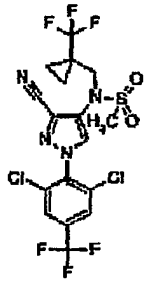


To a solution of Example 36 (104 mg, 0.19 mmol) in tetrahydrofuran (5 ml) was added dropwise *tert*-butyl nitrite (66 µl, 0.56 mmol). The reaction mixture was then heated at reflux for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was purified using an Isolute™ cartridge (silica, 5 g) with gradient elution, dichloromethane : methanol [1 : 0 to 95 : 5]. The appropriate fractions were combined and concentrated to give the crude product. The crude product was dissolved in acetonitrile/water (2 : 1, 1.6 ml) and the solution was purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA II 10µm C18 column) using an acetonitrile : 0.1% trifluoroacetic acid in water gradient [65 : 15 to 95 : 5]. The appropriate fractions were concentrated *in vacuo* to give Example 52 (44 mg).

^{1}H-NMR δ (Acetoned_6): 3.64 - 3.65 (3.0H), 4.94 - 5.00 (2.0H), 8.12 - 8.15 (2.0H), 8.74 - 8.76 (1.0H).

Example 53

N-{3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-{[1-(trifluoromethyl)cyclopropyl]methyl}methanesulfonamide

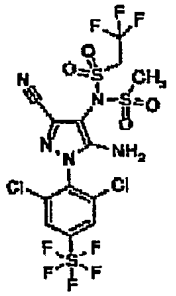


To a solution of Example 33 (62 mg, 0.12 mmol) in tetrahydrofuran (3 ml) was added *tert*-butyl nitrite (30 mg, 0.29 mmol). The reaction mixture was then heated at 60°C for 1 h. The reaction mixture was concentrated *in vacuo* and to the residue was added ethyl acetate (6 ml). The solution was washed with water (6 ml) and the organic phase was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was dissolved in acetonitrile/water (1 : 1, 1 ml) and the solution was purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA II 10μm C18 column) using an acetonitrile : water gradient [60 : 40 to 95 : 5]. The appropriate fractions were concentrated *in vacuo* to give Example 53 (20 mg).

^{1}H-NMR δ (CDCl3): 0.73 - 0.78 (2.0H), 1.01 - 1.05 (2.0H), 3.00 - 3.02 (3.0H), 3.97 - 4.00 (2.0H), 7.74 - 7.78 (2.0H), 7.78 - 7.80 (1.0H).

Example 54

N-{5-amino-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1*H*-pyrazol-4-yl}-*N*-(methylsulfonyl)-2,2,2-trifluoroethanesulfonamide



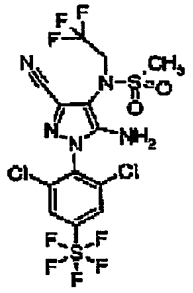
To a solution of Preparation 35 (200 mg, 0.30 mmol) in dioxane (3 ml) was added methanol (1.5 ml) and hydrochloric acid (5N, 1.5 ml). The reaction mixture was then heated at 85°C for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between water (5 ml) and ethyl acetate (10 ml). The two layers were separated and the organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was dissolved in acetonitrile/water (5 : 1, 0.6 ml) and the solution was purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA II 10µm C18 column) using an acetonitrile : water gradient [60 : 40 to 95 : 5]. The appropriate fractions were concentrated *in vacuo* to give Example 54 (48 mg).

MS (ES): M/Z [MH+] 618.0; expected mass for C13H9Cl2F8N5O4S3 + H is 617.9

^{1}H-NMR δ (CDCl3): 3.45 - 3.47 (3.0H), 4.12 - 4.16 (2.0H), 4.31 - 4.37 (1.0H), 4.56 - 4.62 (1.0H), 7.91 - 7.93 (2.0H).

Example 55

N-[5-amino-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1*H*-pyrazol-4-yl]-*N*-(2,2,2-trifluoroethyl)methanesulfonamide

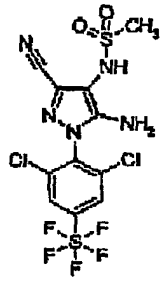


To a solution of Preparation 36 (80 mg, 0.13 mmol) in dioxane (2 ml) and methanol (1 ml) was added hydrochloric acid (5N, 1 ml). The reaction mixture was then heated at 85°C for 18 h. The reaction mixture was concentrated *in vacuo* and

the residue was partitioned between water (5 ml) and ethyl acetate (10 ml). The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was dissolved in a mixture of acetonitrile and water and dimethyl sulphoxide (1 : 2, 1.6 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA C18(2) 10μm column) using an acetonitrile : water gradient [55 : 45 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 55 (43 mg).
MS (ES): M/Z [MH+] 553.9; expected mass for C13H9Cl2F8N5O2S2 + H is 554.0
^{1}H-NMR δ (CDCl3): 3.11 - 3.14 (3.0H), 4.12 - 4.30 (4.0H), 7.90 - 7.93 (2.0H).

Example 56

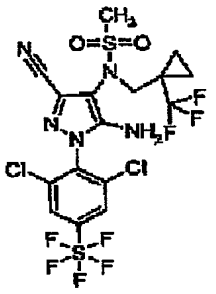
N-{5-amino-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1*H*-pyrazol-4-yl}methanesulfonamide



To a solution of Preparation 37 (121 mg, 0.23 mmol) in dioxane (4 ml) and methanol (1 ml) was added hydrochloric acid (5N, 0.5 ml). The reaction mixture was then heated at 90°C for 5 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (5 ml) and water (5 ml). The two layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 5 ml). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was dissolved in acetonitrile/dimethyl sulphoxide (1 : 1, 0.15 ml) and the solution was purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA II 10μm C18 column) using an acetonitrile : water gradient [50 : 50 to 95 : 5]. The appropriate fractions were concentrated *in vacuo* to give Example 56 (63 mg).
MS (ES): M/Z [MH+] 471.8; expected mass for C11H8Cl2F5N5O2S2 + H is 472.0
^{1}H-NMR δ (CDCl3): 3.10 - 3.13 (3.0H), 4.25 - 4.31 (2.0H), 5.98 - 6.01 (1.0H), 7.89 - 7.92 (2.0H).

Example 57

N-{5-amino-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1*H*-pyrazol-4-yl}-*N*-{[1-(trifluoromethyl)cyclopropyl]methyl}methanesulfonamide



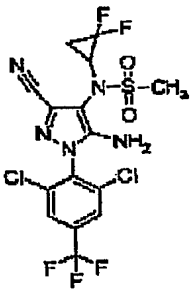
To a solution of Preparation 38 (155 mg, 0.24 mmol) in dioxane (3 ml) and methanol (1 ml) was added hydrochloric acid (5N, 0.5 ml). The reaction mixture was then heated at 90°C for 5 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (6 ml) and water (6 ml). The organic phase was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was dissolved in acetonitrile/dimethyl sulphoxide (1 : 1, 1.2 ml) and the solution was purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA II 10μm C18 column) using an acetonitrile : water gradient [60 : 40 to 95 : 5]. The appropriate fractions were concentrated *in vacuo* to give Example 57 (72 mg).

MS (ES): M/Z [MH+] 593.9; expected mass for C16H13Cl2F8N5O2S2 + H is 593.9

^{1}H-NMR δ (CDCl3): 0.61 - 0.87 (2.0H), 0.99 - 1.06 (2.0H), 3.00 - 3.04 (3.0H), 3.44 - 3.64 (1.0H), [4.14 - 4.38 (3.0H), 7.89 - 7.93 (2.0H).

Example 58

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-(2,2-difluorocyclopropyl)methanesulfonamide



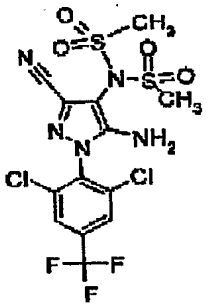
To a solution of Preparation 39 (16 mg, 0.03 mmol) in dioxane (1 ml) and methanol (0.5 ml) was added hydrochloric acid (5N, 0.2 ml). The reaction mixture was then heated at 90°C for 5 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (3 ml) and water (3 ml). The organic phase was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was dissolved in acetonitrile/dimethyl sulphoxide (1 : 1, 1 ml) and the solution was purified by automated preparative liquid chromatography (Gilson system, 150 mm x 30 mm Phenomenex LUNA II 10µm C18 column) using an acetonitrile : water gradient [50 : 50 to 95 : 5]. The appropriate fractions were concentrated *in vacuo* to give Example 58 (2 mg).

MS (ES): M/Z [MH+] 490.0; expected mass for C15H10Cl2F5N5O2S + H is 490.0

^{1}H-NMR δ (CDCl3): 3.13 - 3.16 (3.0H), 3.63 - 3.74 (2.0H), 4.07 - 4.23 (3.0H), 7.75 - 7.79 (2.0H).

Example 59

N-{5-amino-3-cyano-1-[2,6-dichloro-4-trifluoromethylphenyl]-1*H*-pyrazol-4-yl}-*N*-(methylsulfonyl)methanesulfonamide



To a solution of Preparation 40 (200 mg, 0.37 mmol) in methanol (10 ml) was added hydrochloric acid (2N, 10 ml) and the reaction mixture was heated at reflux for 16 h. The reaction mixture was concentrated *in vacuo* and to the residue was

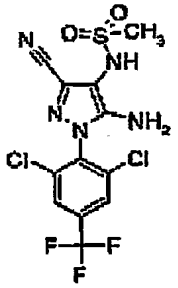
added water (20 ml). The solution was extracted with dichloromethane (2 x 20 ml) and the combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was dissolved in acetonitrile (2 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 21.2 mm Phenomenex LUNA 100Å C18 column) using an acetonitrile : water gradient [50 : 50 to 98 : 2] . The appropriate fractions were concentrated *in vacuo* to give Example 59 (51 mg).

MS (ES): M/Z [MH+] 492.3; expected mass for C13H10Cl2F3N5O4S2 + H is 492.0

^{1}H-NMR δ (CDCl3): 3.43 - 3.45 (6.0H), 7.75 - 7.77 (2.0H).

Example 60

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}methanesulfonamide

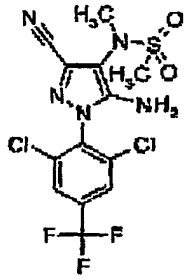


To a solution of Preparation 40 (200 mg, 0.37 mmol) in methanol (10 ml) was added hydrochloric acid (2N, 10 ml) and the reaction mixture was heated at reflux for 16 h. The reaction mixture was concentrated *in vacuo* and to the residue was added water (20 ml). The solution was extracted with dichloromethane (2 x 20 ml) and the combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was dissolved in acetonitrile (2 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 21.2 mm Phenomenex LUNA 100Å C18 column) using an acetonitrile : water gradient [50 : 50 to 98 : 2] . The appropriate fractions were concentrated *in vacuo* to give Example 60 (18 mg).

^{1}H-NMR δ (CD3OD): 3.02 - 3.07 (3.0H), 7.97 - 8.02 (2.0H).

Example 61

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-methylmethanesulfonamide



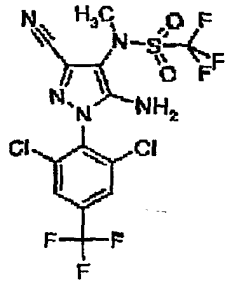
To a solution of Preparation 41 (370 mg, 0.77 mmol) in methanol (10 ml) was added hydrochloric acid (4N, 3 ml) and the reaction mixture was heated at reflux for 4 h. The reaction mixture was concentrated *in vacuo* and to the residue was added ethyl acetate and water. The aqueous layer was separated and extracted with ethyl acetate (x 3) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (silica, 20 g) with gradient elution, cyclohexane : dichloromethane [1 : 1 to 0 : 1], followed by dichloromethane : methanol [1 : 0 to 9 : 1]. The appropriate fractions were combined and concentrated to give Example 61 (160 mg, 49%).

MS (ES): M/Z [MH+] 427.9; expected mass for C13H10Cl2F3N5O2S + H is 428.0

^{1}H-NMR δ (DMSOd_6): 3.01 - 3.08 (3.0H), 3.17 - 3.22 (3.0H), 6.37 - 6.45 (2.0H), 8.21 - 8.27 (2.0H).

Example 62

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-methyl-1,1,1-trifluoromethanesulfonamide



Precursors used to synthesise Example 62: Preparation 42

Reaction: Method 1

Workup: Method 3

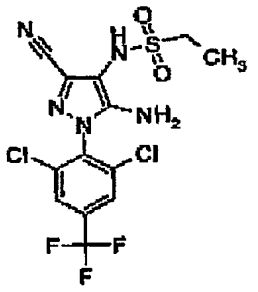
The crude product was dissolved in acetonitrile (4 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 21.2 mm Phenomenex LUNA 100Å C18 column) using an acetonitrile : water gradient [50 : 50 to 98 : 2] . The appropriate fractions were concentrated *in vacuo* to give Example 62 (105 mg).

MS (ES): M/Z [MH+] 482.0; expected mass for C13H7Cl2F6N5O2S + H is 482.0

^{1}H-NMR δ (CDCl3): 3.50 - 3.52 (3.0H), 4.00 - 4.10 (2.0H), 7.71 - 7.76 (2.0H).

Example 63

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}ethanesulfonamide



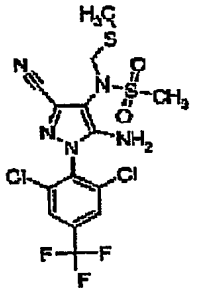
To a solution of Preparation 43 (200 mg) in methanol (4 ml) was added hydrochloric acid (4M, 3 ml). The reaction mixture was then heated at 90°C for 12 h. The reaction mixture was concentrated *in vacuo* and to the residue was added water (15 ml). This solution was neutralised by addition of saturated aqueous sodium hydrogen carbonate and then extracted with dichloromethane (3 x 10 ml). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved in acetonitrile (4 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 21.2 mm Phenomenex LUNA 100Å C18 column) using an acetonitrile : water gradient [10 : 90 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 63 (196 mg).

MS (ES): M/Z [MH+] 428.2; expected mass for C13H10Cl2F3N5O2S + H is 428.0

^{1}H-NMR δ (CD3OD): 1.39 - 1.45 (3.0H), 3.10 - 3.17 (2.0H), 7.96 - 8.00 (2.0H).

Example 64

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-*N*-[(methylthio)methyl]methanesulfonamide



Precursors used to synthesise Example 64: Preparation 53

Reaction: Method 1

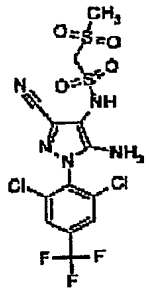
Workup: Method 1

The crude product was dissolved in acetonitrile (4 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 21.2 mm Phenomenex LUNA 100 Å C18 column) using an acetonitrile : water gradient [10 : 90 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 64 (109 mg).

^{1}H-NMR δ (CDCl3): 2.23 - 2.25 (3.0H), 3.10 - 3.12 (3.0H), 4.21 - 4.25 (2.0H), 4.76 - 4.80 (2.0H), 7.77 - 7.78 (2.0H).

Example 65

N-{5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}-1-(methylsulfonyl)methanesulfonamide



To a solution of Preparation 55 (200 mg) in methanol (4 ml) was added hydrochloric acid (4M, 3 ml). The reaction mixture was then heated at 80°C for 24

h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between water (20 ml) and dichloromethane (20 ml). The two layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 20 ml). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was dissolved in acetonitrile (4.5 ml) and purified by automated preparative liquid chromatography (Gilson system, 150 mm x 21.2 mm Phenomenex LUNA 100Å C18 column) using an acetonitrile : water gradient [10 : 90 to 95 : 5] . The appropriate fractions were concentrated *in vacuo* to give Example 65 (90 mg).

MS (ES): M/Z [MH+] 491.9; expected mass for C13H10Cl2F3N5O4S2 + H is 492.0

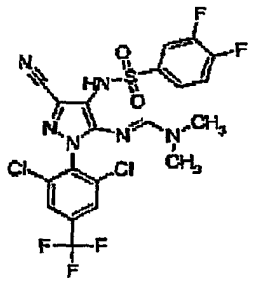
^{1}H-NMR δ (DMSOd_6): 3.19 - 3.22 (3.0H), 4.98 - 5.03 (2.0H), 6.19 - 6.28 (2.0H), 8.19 - 8.25 (2.0H), 9.83 - 9.87 (1.0H).

PREPARATIONS

The following Preparations illustrate the synthesis of certain intermediates used in the preparation of the preceding Examples.

Preparation 1

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-3,4-difluorobenzenesulfonamide

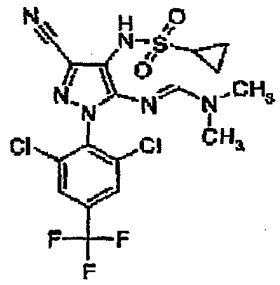


To a solution of Preparation 50 (200 mg, 0.51 mmol) in dichloromethane (4 ml) was added 4-dimethylaminopyridine (20 mg), pyridine (0.2 ml) and 3,4-difluorobenzenesulphonyl chloride (163 mg, 0.77 mmol). The reaction mixture was then stirred at room temperature for 18 h. The reaction mixture was concentrated under a stream of nitrogen to give Preparation 1 (200 mg), as a mixture of mono- and bis-sulphonated product.

MS (ES): M/Z [MH+] 567.1; expected mass for C20H13Cl2F5N6O2S + H is 567.0

Preparation 2

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)cyclopropanesulfonamide



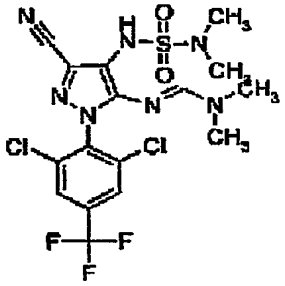
To a solution of Preparation 50 (200 mg, 0.51 mmol) in dichloromethane (3 ml) was added pyridine (0.2 ml), 4-dimethylaminopyridine (catalytic amount) and Preparation 51 (107 mg, 0.77 mmol). The reaction mixture was then stirred for 18

h at room temperature. The reaction mixture was concentrated *in vacuo* to give Preparation 2 (200 mg).

MS (ES): M/Z [MH+] 495.1; expected mass for C17H15Cl2F3N6O2S + H is 495.0

Preparation 3

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-{[(dimethylamino)sulfonyl]amino}-1*H*-pyrazol-5-yl)-*N*,*N*-dimethylimidoformamide



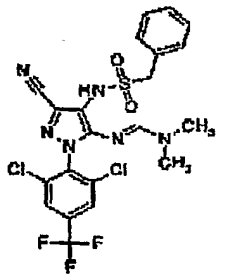
To dimethylsulphamoyl chloride (81 µl, 0.75 mmol) was added a solution of Preparation 50 (200 mg, 0.51 mmol), 4-dimethylaminopyridine (20 mg) and pyridine (0.2 ml) in dichloromethane (4 ml). The reaction mixture was then stirred for 18 h at room temperature. The reaction mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane (10 ml) and hydrochloric acid (1M, 10 ml). The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified using an Isolute™ column (silica, 10 g) with gradient elution, ethyl acetate : cyclohexane [1 : 3 to 1 : 1]. The appropriate fractions were combined and concentrated to give Preparation 3 (193 mg).

MS (ES): M/Z [MH+] 498.3; expected mass for C16H16Cl2F3N7O2S + H is 498.1

^{1}H-NMR δ (CDCl3):2.74 - 2.78 (3.0H), 2.93 - 2.97 (6.0H), 3.02 - 3.06 (3.0H), 5.96 - 6.00 (1.0H), 7.64 - 7.68 (2.0H), 8.52 - 8.54 (1.0H).

Preparation 4

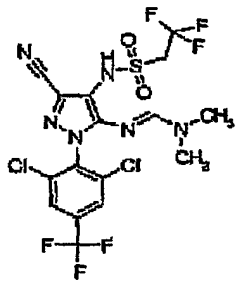
N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-1-phenylmethanesulfonamide



To a solution of Preparation 50 (200 mg, 0.51 mmol) in dichloromethane (4 ml) was added 4-dimethylaminopyridine (20 mg), pyridine (0.2 ml) and benzylsulphonyl chloride (145 mg, 0.76 mmol). The reaction mixture was then stirred at room temperature for 18 h. The reaction mixture was concentrated under a stream of nitrogen to give Preparation 4 (145 mg), as a mixture of mono-sulphonated product and starting material.

Preparation 5

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-2,2,2-trifluoroethanesulfonamide

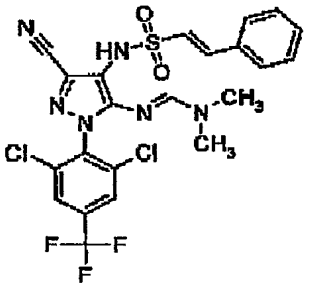


To a solution of Preparation 50 (200 mg, 0.51 mmol) in dichloromethane (4 ml) was added 4-dimethylaminopyridine (20 mg), pyridine (0.2 ml) and 2,2,2-trifluoroethylsulphonyl chloride (140 mg, 0.76 mmol). The reaction mixture was then stirred at room temperature for 18 h. The reaction mixture was concentrated under a stream of nitrogen to give Preparation 5 (200 mg), as a mixture of mono- and bis-sulphonated product.

MS (ES): M/Z [MH+] 537.1; expected mass for C16H12Cl2F6N6O2S + H is 537.0

Preparation 6

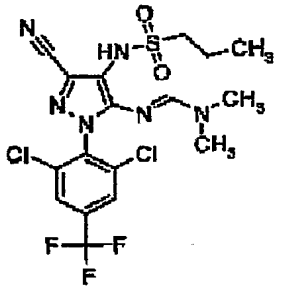
(*E*)-*N*-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-2-phenylethylenesulfonamide



To a solution of Preparation 50 (200 mg, 0.51 mmol) in dichloromethane (4 ml) was added 4-dimethylaminopyridine (20 mg), pyridine (0.2 ml) and *beta*-styrene sulphonyl chloride (155 mg, 0.76 mmol). The reaction mixture was then stirred at room temperature for 18 h. The reaction mixture was concentrated under a stream of nitrogen to give Preparation 6 (155 mg), as a mixture of mono-sulphonated product and starting material.

Preparation 7

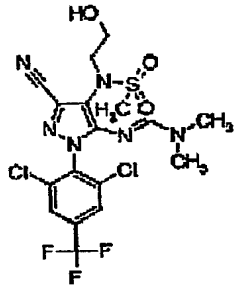
N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)propane-1-sulfonamide



To a solution of Preparation 50 (200 mg, 0.51 mmol) in dichloromethane (4 ml) was added 4-dimethylaminopyridine (20 mg), pyridine (0.2 ml) and 1-propanesulphonyl chloride (102 mg, 0.72 mmol). The reaction mixture was then stirred at room temperature for 18 h. The reaction mixture was concentrated under a stream of nitrogen to give Preparation 7 (109 mg, 0.22 mmol), as the mono-sulphonated product.

Preparation 8

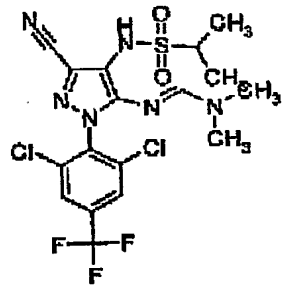
N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-*N*-(2-hydroxyethyl)methanesulfonamide



To a solution of the sulphonamide (200 mg, 0.43 mmol), Preparation 19, in acetone (7 ml) was added potassium carbonate (88 mg, 0.64 mmol), followed by 2-iodoethanol (50 µl, 0.64 mmol). The reaction mixture was then heated at reflux for 2 h. The reaction mixture was concentrated under nitrogen and the residue partitioned between ethyl acetate and water. The two layers were separated and the aqueous layer was extracted with ethyl acetate (x 2). The combined organic phases were dried ($MgSO_4$) and concentrated under nitrogen to give Preparation 8 (257 mg).

Preparation 9

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)propane-2-sulfonamide

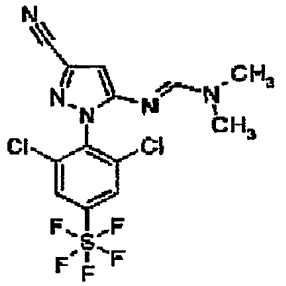


To a solution of Preparation 50 (200 mg, 0.51 mmol) in pyridine (5 ml), at 0°C, was added dropwise isopropyl sulphonyl chloride (115 µl, 1.03 mmol). The reaction mixture was stirred for 18 h at room temperature and further isopropyl sulphonyl

chloride (57.5 µl, 0.5 mmol) was added. The reaction mixture was then stirred at room temperature for another 18 h. The reaction mixture was acidified with hydrochloric acid (2N) and then partitioned between dichloromethane (20 ml) and hydrochloric acid (1N, 20 ml). The organic layer was separated, washed with hydrochloric acid (1N, 2 x 20 ml) and water (20 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography with gradient elution, cyclohexane : ethyl acetate [3 : 1 to 0 : 1]. The appropriate fractions were combined and concentrated to give Preparation 9 (186 mg).

Preparation 10

N-[3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1*H*-pyrazol-5-yl]-*N*,*N*-dimethylimidoformamide



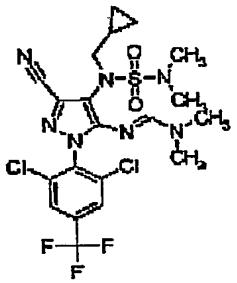
To a solution of Preparation 47 (2.2 g, 3.9 mmol) in dry tetrahydrofuran (30 ml), at -30°C, was added isopropylmagnesium chloride (2M in *N*,*N*-dimethylformamide, 2.2 ml, 4.4 mmol). The reaction mixture was then allowed to warm to room temperature over 1 h. To the reaction mixture was added saturated aqueous ammonium chloride solution (10 ml) and ethyl acetate (excess). The organic layer was separated, washed with saturated brine solution, dried ($MgSO_4$) and concentrated *in vacuo* to give Preparation 10 (1.6 g).

MS (ES): M/Z [MH+] 433.8; expected mass for C13H10Cl2F5N5S + H is 434.0

^{1}H-NMR δ (CDCl3): 2.74 - 2.82 (3.0H), 2.98 - 3.04 (3.0H), 6.11 - 6.18 (1.0H), 7.69 - 7.75 (1.0H), 7.75 - 7.83 (2.0H).

Preparation 11

N-[3-cyano-4-[(cyclopropylmethyl)[(dimethylamino)sulfonyl]amino]-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-5-yl]-*N*,*N*-dimethylimidoformamide

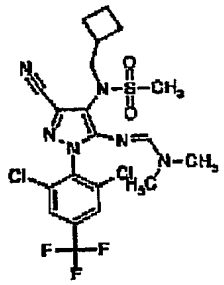


To a suspension of Preparation 3 (90 mg, 0.18 mmol) and potassium carbonate (50 mg, 0.36 mmol) in acetone (3 ml) was added (bromomethyl)cyclopropane (18 µl, 0.18 mmol). The reaction mixture was stirred for 18 h and additional (bromomethyl)cyclopropane (18 µl, 0.18 mmol) was added. The reaction mixture was then stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between water (10 ml) and dichloromethane (10 ml). The organic layer was separated, dried (Na_2SO_4) and concentrated *in vacuo* to give Preparation 11 (90 mg).

^{1}H-NMR δ (CDCl3): 0.06 - 0.14 (2.0H), 0.39 - 0.48 (2.0H), 0.67 - 0.78 (1.0H), 2.68 - 2.72 (3.0H), 2.92 - 2.97 (6.0H), 2.97 - 3.00 (3.0H), 7.61 - 7.69 (2.0H), 8.46 - 8.53 (1.0H).

Preparation 12

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-*N*-(cyclobutylmethyl)methanesulfonamide

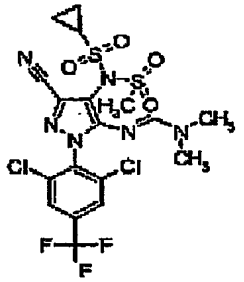


To a solution of Preparation 19 (100 mg, 0.21 mmol) in acetone (4 ml) was added potassium carbonate (47 mg, 0.34 mmol), followed by (bromomethyl)cyclobutane (48 mg, 0.32 mmol). The reaction mixture was then heated at reflux for 2 h. The

reaction mixture was concentrated under nitrogen and the residue was partitioned between ethyl acetate and water. The two layers were separated and the aqueous layer was extracted with ethyl acetate (x 2). The combined organic phases were dried ($MgSO_4$) and concentrated under nitrogen to give Preparation 12 (102 mg).

Preparation 13

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-*N*-(methylsulfonyl)cyclopropanesulfonamide

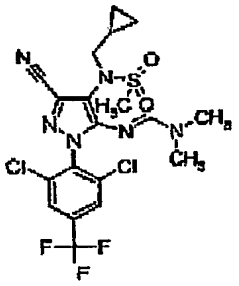


To a solution of Preparation 19 (150 mg, 0.32) and triethylamine (66 µl, 0.48 mmol) in dichloromethane (3 ml) was added cyclopropanesulphonyl chloride (35 mg, 0.48 mmol). The reaction mixture was then stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was purified using an Isolute™ cartridge (silica, 10 g) with gradient elution, cyclohexane : ethyl acetate [3 : 1 to 1 : 1] . The appropriate fractions were combined and concentrated to give Preparation 13 (150 mg).

MS (ES): M/Z [MH+] 572.9; expected mass for C18H17Cl2F3N6O4S2 + H is 573.0

Preparation 14

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-*N*-(cyclopropylmethyl)methanesulfonamide



Precursors used to synthesise Preparation 14: Preparation 19, cyclopropylmethyl bromide

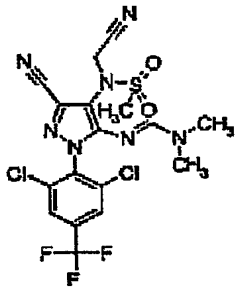
Reaction: Method 3

Workup: Method 3

MS (ES): M/Z [MH+] 523.4; expected mass for C19H19Cl2F3N6O2S + H is 523.1

Preparation 15

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-*N*-(cyanomethyl)methanesulfonamide



Precursors used to synthesise Preparation 15: Preparation 19, bromoacetonitrile

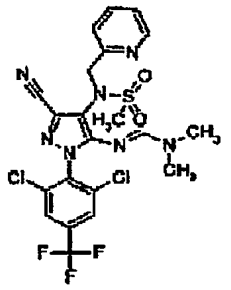
Reaction: Method 3

Workup: Method 3

MS (ES): M/Z [MH+] 508.3; expected mass for C17H14Cl2F3N7O2S + H is 508.0

Preparation 16

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-*N*-(pyridin-2-ylmethyl)methanesulfonamide

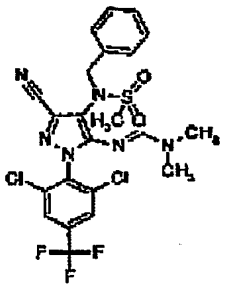


To a solution of the sulphonamide, Preparation 19, (100 mg, 0.21 mmol) in acetone (4 ml) was added potassium carbonate (77 mg, 0.55 mmol), followed by 2-(bromomethyl)pyridine hydrobromide (65 mg, 0.26 mmol). The reaction mixture was then heated at reflux for 2 h. The reaction mixture was concentrated under nitrogen and the residue partitioned between ethyl acetate and water. The two layers were separated and the aqueous layer was extracted with ethyl acetate (x 2). The combined organic phases were dried ($MgSO_4$) and concentrated under nitrogen to give Preparation 16 (100 mg).

MS (ES): M/Z [MH+] 560.4; expected mass for C21H18Cl2F3N7O2S + H is 560.1

Preparation 17

N-benzyl-*N*-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)methanesulfonamide



Precursors used to synthesise Preparation 17: Preparation 19, benzyl bromide

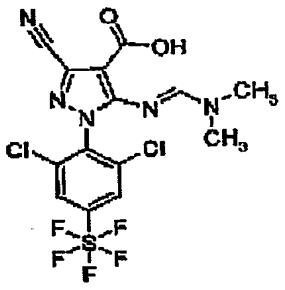
Reaction: Method 3

Workup: Method 3

MS (ES): M/Z [MH+] 559.4; expected mass for C22H19Cl2F3N6O2S + H is 559.1

Preparation 18

3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazole-4-carboxylic acid

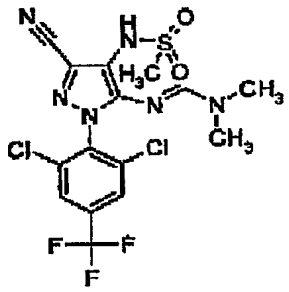


To a solution of Preparation 46 (8.0 g, 16.25 mmol) in anhydrous pyridine (80 ml) was added lithium iodide (10.9 g, 81.25 mmol). The reaction mixture was then heated at reflux, under nitrogen, for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (200 ml) and hydrochloric acid (2N, 200 ml). The organic layer was separated, washed with hydrochloric acid (2N, 2 x 200 ml) and brine (200 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (silica, 300 g) with gradient elution, methanol : dichloromethane [0.5 : 95.5 to 10 : 90]. The appropriate fractions were combined and concentrated to give Preparation 18 (6.7 g).

MS (ES): M/Z [MH+] 477.8; expected mass for C14H10Cl2F5N5O2S + H is 478.0

Preparation 19

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)methanesulfonamide



To Preparation 40 (3.4 g, 6.21 mmol) in a mixture of tetrahydrofuran (35 ml) and methanol (35 ml) was added potassium carbonate (2.15 g, 15.53 mmol). The reaction mixture was then stirred at room temperature for 2 h. The reaction mixture was concentrated *in vacuo* and to the residue was added ethyl acetate. The solution was washed with hydrochloric acid (1N) and brine and then concentrated *in vacuo*. The residue was purified by column chromatography (silica, 50 g) with gradient elution, dichloromethane : methanol [100 : 0 to 95 : 5]. The appropriate fractions were combined and concentrated to give Preparation 19 (620 mg).

^{1}H-NMR δ ($DMSOd_6$): 2.67 - 2.70 (3.0H), 2.90 - 2.95 (3.0H), 2.99 - 3.02 (3.0H), 8.19 - 8.23 (2.0H), 8.30 - 8.33 (1.0H), 9.43 - 9.47 (1.0H).

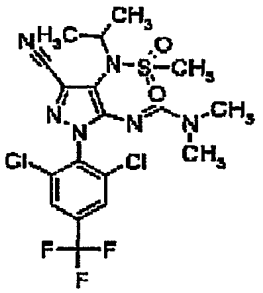
Alternative preparation

To a solution of Preparation 40 (677 mg, 1.24 mmol) in tetrahydrofuran (7 ml), at 0°C, was added potassium carbonate (427 mg, 3.09 mmol) in methanol (7 ml), containing a small amount of water. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was concentrated *in vacuo* and to the residue was added dichloromethane. The solution was washed with hydrochloric acid (1N) and the organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give Preparation 19 (573 mg, 99%).

MS (ES): M/Z [MH+] 469.3; expected mass for C15H13Cl2F3N6O2S + H is 469.0

Preparation 20

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-*N*-isopropylmethanesulfonamide

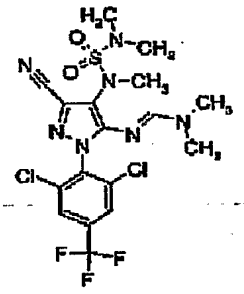


To a solution of the sulphonamide (200 mg, 0.43 mmol), Preparation 19, in acetone (7 ml) was added potassium carbonate (88 mg, 0.64 mmol), followed by 2-iodopropane (64 µl, 0.64 mmol). The reaction mixture was then heated at reflux for 2 h. The reaction mixture was concentrated under nitrogen and the residue partitioned between ethyl acetate and water. The two layers were separated and the aqueous layer was extracted with ethyl acetate (x 2). The combined organic phases were dried ($MgSO_4$) and concentrated under nitrogen to give Preparation 20 (242 mg).

MS (ES): M/Z [MH+] 511.4; expected mass for C18H19Cl2F3N6O2S + H is 511.1

Preparation 21

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-{[(dimethylamino)sulfonyl](methyl)amino}-1*H*-pyrazol-5-yl)-*N*,*N*-dimethylimidoformamide



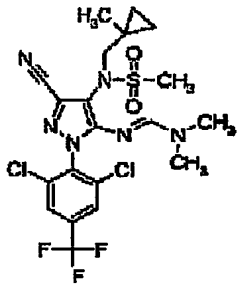
To a solution of Preparation 3 (90 mg, 0.18 mmol) and methyl iodide (11 µl, 0.18 mmol) was added potassium carbonate (50 mg, 0.36 mmol). The reaction mixture was then stirred at room temperature for 18 h. The reaction mixture was concentrated under a stream of nitrogen and the residue was partitioned between water (5 ml) and dichloromethane (5 ml). The two layers were separated and the aqueous layer was re-extracted with dichloromethane (2 x 5 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give Preparation 21 (90 mg).

MS (ES): M/Z [MH+] 512.3; expected mass for C17H18Cl2F3N7O2S + H is 512.1

^{1}H-NMR δ (CDCl3): 2.71 - 2.75 (3.0H), 2.98 - 3.01 (6.0H), 3.21 - 3.24 (3.0H), 7.64 - 7.68 (2.0H), 8.39 - 8.42 (1.0H).

Preparation 22

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-*N*-[(1-methylcyclopropyl)methyl]methanesulfonamide

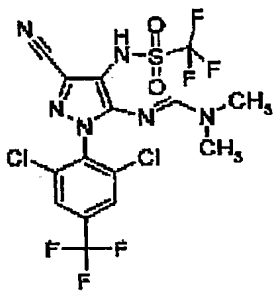


To a mixture of 1-methylcyclopropanemethanol (0.11 ml, 1.16 mmol), triethylamine (0.22 ml, 1.54 mmol) and 4-dimethylaminopyridine (14 mg, 0.12 mmol) in dichloromethane (5 ml) was added dropwise methanesulphonyl chloride (84 µl, 1.08 mmol). The reaction mixture was stirred at room temperature for 2 h and then concentrated *in vacuo*. The residue was dissolved in acetone (4 ml) and any solid material removed by filtration. This solution was added to a mixture of Preparation 19 (130 mg, 0.28 mmol), potassium carbonate (80 mg, 0.58 mmol) and potassium iodide (5 mg, 0.03 mmol) in *N,N*-dimethylformamide (2.5 ml). The reaction mixture was then heated under nitrogen at 80°C for 1 h. To the reaction mixture was added hydrochloric acid (1N, 6 ml) and the mixture was extracted with ethyl acetate (2 x 6 ml). The combined extracts were washed with water (10 ml) and brine (10 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give Preparation 22 (149 mg).

MS (ES): M/Z [MH+] 537.4; expected mass for C20H21Cl2F3N6O2S + H is 537.1

Preparation 23

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-1,1,1-trifluoromethanesulfonamide

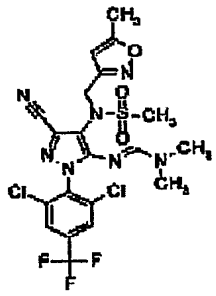


To a solution of Preparation 58 (650 mg, 0.99 mmol) in trifluoroethanol (9 ml) was added aqueous sodium hydroxide solution (2.5N, 16 drops). The reaction mixture was then stirred at room temperature, under nitrogen, for 1 h. To the reaction mixture was added hydrochloric acid (2M, 2 ml) and the solution was concentrated *in vacuo*. The residue was partitioned between ethyl acetate (20 ml) and water (20 ml) and the two phases were separated. The organic phase was washed with water (2 x 20 ml), dried (Na_2SO_4) and concentrated *in vacuo* to give Preparation 23 (505 mg, 98%).

MS (ES): M/Z [MH+] 523.2; expected mass for C15H10Cl2F6N6O2S + H is 523.0

Preparation 24

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-[[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-*N*-[(5-methylisoxazol-3-yl)methyl]methanesulfonamide

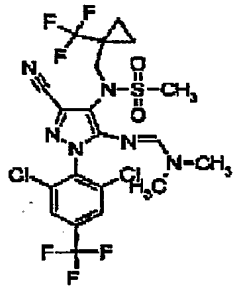


To a solution of Preparation 19 (200 mg, 0.43 mmol) in acetone (5 ml) was added Preparation 59 (163 mg, 0.85 mmol) and potassium carbonate (118 mg, 0.86 mmol). The reaction mixture was then heated at 90°C for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between water and dichloromethane. The two layers were separated and the aqueous layer was extracted with dichloromethane (x 3). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give Preparation 24 (263 mg).

MS (ES): M/Z [MH+] 564.0; expected mass for C20H18Cl2F3N7O3S + H is 564.1

Preparation 25

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-*N*-{[1-(trifluoromethyl)cyclopropyl]methyl}methanesulfonamide



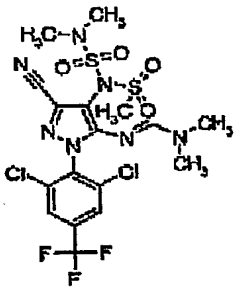
To a solution of Preparation 19 (100 mg, 0.21 mmol) in acetone (4 ml) was added potassium carbonate (47 mg, 0.34 mmol), followed by Preparation 60 (94 mg, 0.32 mmol). The reaction mixture was then heated at reflux for 2 h. The reaction mixture was concentrated under nitrogen and the residue was partitioned between ethyl acetate and water. The two layers were separated and the aqueous layer was extracted with ethyl acetate (x 2). The combined organic phases were dried ($MgSO_4$) and concentrated under nitrogen to give Preparation 25 (150 mg).

MS (ES): M/Z [MH+] 591.0; expected mass for C20H18Cl2F6N6O2S + H is 591.1

^{1}H-NMR δ (CDCl3): 0.50 - 0.65 (2.0H), 0.90 - 0.99 (2.0H), 2.72 - 2.77 (3.0H), 2.97 - 3.01 (3.0H), 3.14 - 3.18 (3.0H), 3.29 - 3.37 (1.0H), 4.27 - 4.38 (1.0H), 7.64 - 7.74 (2.0H), 8.46 - 8.50 (1.0H).

Preparation 26

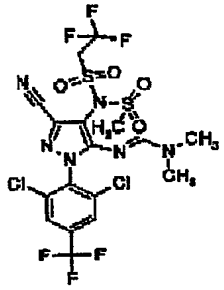
N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-*N*-[(dimethylamino)sulfonyl]methanesulfonamide



To a solution of Preparation 19 (150 mg, 0.32) and triethylamine (66 µl, 0.48 mmol) in dichloromethane (3 ml) was added dimethylsulphamoyl chloride (51 µl, 0.48 mmol). The reaction mixture was then stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo* to give Preparation 26 (150 mg). MS (ES): M/Z [MH+] 575.9; expected mass for C17H18Cl2F3N7O4S2 + H is 576.0

Preparation 27

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-*N*-(methylsulfonyl)-2,2,2-trifluoroethanesulfonamide



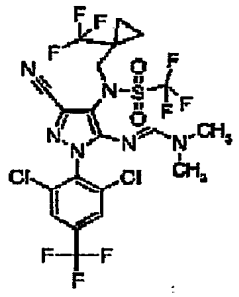
To a solution of Preparation 19 (150 mg, 0.32) and triethylamine (66 µl, 0.48 mmol) in dichloromethane (3 ml) was added 2,2,2-trifluoroethylsulphonyl chloride (35 µl, 0.48 mmol). The reaction mixture was stirred at room temperature for 18 h and further 2,2,2-trifluoroethylsulphonyl chloride (60 µl, 0.64 mmol) was added. The reaction mixture was then stirred for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was purified using an Isolute™ cartridge (silica, 10 g) with gradient elution, dichloromethane : methanol [1 : 0 to 95 : 5]. The appropriate fractions were combined and concentrated to give Preparation 27 (70 mg).

MS (ES): M/Z [MH+] 614.9; expected mass for C17H14Cl2F6N6O4S2 + H is 615.0

^{1}H-NMR δ (CDCl3): 2.78 - 2.83 (3.0H), 2.98 - 3.03 (3.0H), 3.43 - 3.48 (3.0H), 4.37 - 4.45 (2.0H), 7.64 - 7.75 (2.0H), 7.83 - 7.87 (1.0H).

Preparation 28

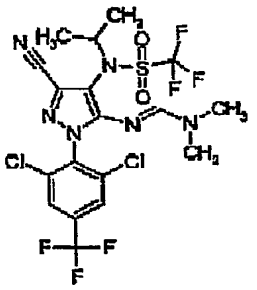
N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-*N*-{[1-(trifluoromethyl)cyclopropyl]methyl}-1,1,1-trifluoromethanesulfonamide



To a solution of Preparation 23 (200 mg, 0.38 mmol) in acetone (4 ml) was added potassium carbonate (106 mg, 0.76 mmol), followed by Preparation 60 (135 mg, 0.46 mmol). The reaction mixture was heated at reflux for 7 days and further Preparation 60 (112 mg, 0.38 mmol) was added. The reaction mixture was then heated at reflux for 18 h. The reaction mixture was concentrated under a stream of nitrogen and the residue was partitioned between dichloromethane (20 ml) and water (20 ml). The organic layer was separated, washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with cyclohexane/ethyl acetate [3 : 2]. The appropriate fractions were combined and concentrated to give Preparation 28 (200 mg).

Preparation 29

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-*N*-isopropyl-1,1,1-trifluoromethanesulfonamide

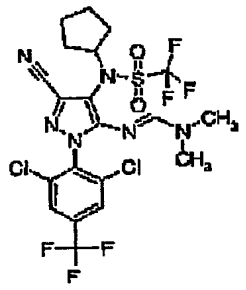


To a mixture of Preparation 23 (100 mg, 0.19 mmol) and potassium carbonate (26 mg, 0.19 mmol) in acetone (4 ml) was added 2-iodopropane (32 mg, 0.19 mmol). The reaction mixture was stirred at room temperature for 18 h and further 2-iodopropane (32 mg, 0.19 mmol) was added. The reaction mixture was then stirred at room temperature for 7 days. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between water (25 ml) and dichloromethane (25 ml). The two layers were separated and the aqueous layer was extracted with ethyl acetate (25 ml). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified using an Isolute™ cartridge (silica, 25 g) with gradient elution, dichloromethane : methanol [1 : 0 to 95 : 5]. The appropriate fractions were combined and concentrated to give Preparation 29 (59 mg).

^{1}H-NMR δ (CDCl3): 1.07 - 1.13 (3.0H), 1.32 - 1.37 (3.0H), 2.74 - 2.79 (3.0H), 2.97 - 3.02 (3.0H), 4.42 - 4.51 (1.0H), 7.61 - 7.74 (2.0H), 7.98 - 8.01 (1.0H).

Preparation 30

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-*N*-cyclopentyl-1,1,1-trifluoromethanesulfonamide



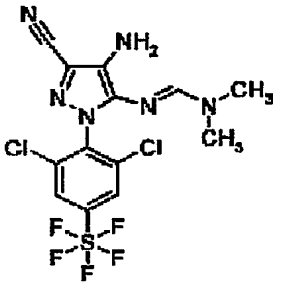
To a mixture of Preparation 23 (100 mg, 0.19 mmol) and potassium carbonate (26 mg, 0.19 mmol) in acetone (4 ml) was added iodocyclopentane (37 mg, 0.19 mmol). The reaction mixture was stirred at room temperature for 18 h and further iodocyclopentane (32 mg, 0.19 mmol) was added. The reaction mixture was then stirred at room temperature for 7 days. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between water (25 ml) and dichloromethane (25 ml). The two layers were separated and the aqueous layer was extracted with ethyl acetate (25 ml). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified using an Isolute™ cartridge (silica, 25 g) with gradient elution, dichloromethane : methanol [1 : 0 to 95 : 5]. The appropriate fractions were combined and concentrated to give Preparation 30 (63 mg).

MS (ES): M/Z [MH+] 590.9; expected mass for C20H18Cl2F6N6O2S + H is 591.1

^{1}H-NMR δ (CDCl3): 1.42 - 1.56 (4.0H), 1.60 - 1.69 (2.0H), 1.74 - 1.83 (1.0H), 2.06 - 2.17 (1.0H), 2.75 - 2.78 (3.0H), 2.98 - 3.02 (3.0H), 4.42 - 4.51 (1.0H), 7.64 - 7.71 (2.0H), 8.03 - 8.07 (1.0H).

Preparation 31

N'-[4-amino-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-1*H*-pyrazol-5-yl]-*N*,*N*-dimethylimidoformamide



To a solution of Preparation 61 (9.0 g, 15.15 mmol) in tetrahydrofuran (120 ml) was added tetrabutylammonium fluoride (60.6 ml, 60.6 mmol) over 5 min. The reaction mixture was heated at 50°C for 1 h and then allowed to cool to room temperature. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (200 ml) and water (200 ml). The organic layer was separated, washed with water (2 x 200 ml) and brine (200 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography

(silica, 250 g) with gradient elution, ethyl acetate : dichloromethane [0 : 1 to 1 : 4]. The appropriate fractions were combined and concentrated to give Preparation 31 (2.6 g).

MS (ES): M/Z [MH+] 449.0; expected mass for C13H11Cl2F5N6S + H is 449.0

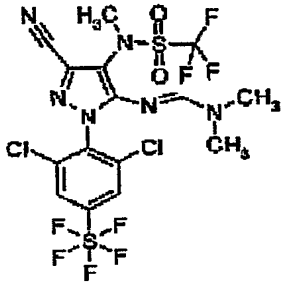
Alternative synthesis

A solution of Preparation 62 (10.0 g, 21.0 mmol) in methanol (300 ml) was placed under a hydrogen atmosphere (50 psi), with platinum (5% on charcoal, 1 g), at room temperature for 2 h. The reaction mixture was filtered and concentrated *in vacuo* and the residue was triturated with diethyl ether. The solution was concentrated *in vacuo* to give Preparation 31 (8.5 g).

^{1}H-NMR δ (CDCl3): 2.74 - 2.78 (3.0H), 2.96 - 2.99 (3.0H), 7.76 - 7.81 (2.0H), 8.18 - 8.21 (1.0H).

Preparation 32

N-(3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-*N*-methyl-1,1,1-trifluoromethanesulfonamide

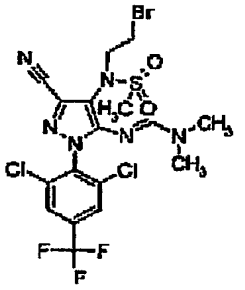


To a solution of Preparation 63 (200 mg, 0.34 mmol) in acetone (4 ml) was added potassium carbonate (119 mg, 0.86 mmol) and methyl iodide (21.4 µl, 0.34 mmol). The reaction mixture was then stirred at room temperature for 18 h. The reaction mixture was concentrated under a stream of nitrogen and the residue was partitioned between dichloromethane (30 ml) and water (30 ml). The organic layer was separated, washed with water (2 x 30 ml), dried (Na_2SO_4) and concentrated *in vacuo* to give Preparation 32, which was used directly.

MS (ES): M/Z [MH+] 594.9; expected mass for C15H12Cl2F8N6O2S2 + H is 595.0

Preparation 33

N-(2-bromoethyl)-*N*-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)methanesulfonamide

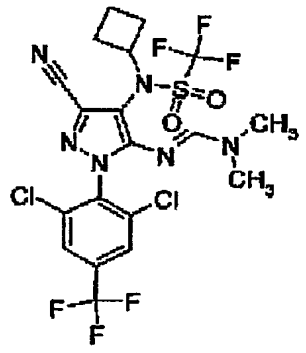


A mixture of Preparation 19 (373 mg, 0.80 mmol), caesium carbonate (390 mg, 1.20 mmol) and 1,2-dibromoethane (0.34 ml, 4.0 mmol) in acetonitrile (15 ml) was heated at reflux for 18 h. The reaction mixture was cooled and poured into ice/water (20 ml). The mixture was extracted with ethyl acetate (2 x 20 ml) and the combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (silica) with gradient elution, hexane : ethyl acetate [4 : 1 to 2 : 1]. The appropriate fractions were combined and concentrated to give Preparation 33 (414 mg).

MS (ES): M/Z [MH+] 575.0; expected mass for C17H16BrCl2F3N6O2S + H is 575.0

Preparation 34

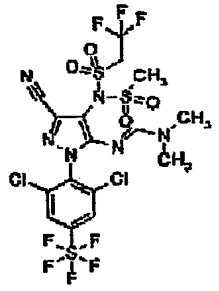
N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-*N*-cyclobutyl-1,1,1-trifluoromethanesulfonamide



To a solution of Preparation 23 (1.0 g, 1.91 mmol) in acetone (15 ml) was added cyclobutyl bromide (180 µl, 1.91 mmol) and potassium carbonate (260 mg, 1.91 mmol). The reaction mixture was heated at reflux for 18 h and further cyclobutyl bromide (360 µl, 3.82 mmol) was added. The reaction mixture was then heated at reflux for another 8 days. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (50 ml) and water (50 ml). The two layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 50 ml). The combined organic phases were then dried and concentrated *in vacuo*.
Purification: The residue was purified using an Isolute™ cartridge (silica, 50 g) with gradient elution, dichloromethane : methanol [1 : 0 to 95 : 5]. The appropriate fractions were combined and concentrated to give Preparation 34 (300 mg).
MS (ES): M/Z [MH+] 577.0; expected mass for C19H16Cl2F6N6O2S + H is 577.0
^{1}H-NMR δ (CDCl3): 0.16 - 0.24 (2.0H), 0.47 - 0.60 (2.0H), 0.94 - 1.02 (1.0H), 2.76 - 2.77 (3.0H), 3.00 - 3.03 (3.0H), 3.42 - 3.52 (1.0H), 3.62 - 3.71 (1.0H), 7.66 - 7.70 (2.0H), 8.22 - 8.25 (1.0H).

Preparation 35

N-(3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-*N*-(methylsulfonyl)-2,2,2-trifluoroethanesulfonamide



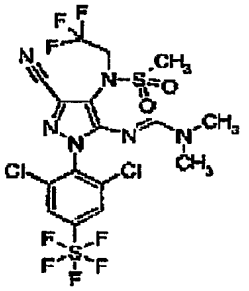
To a solution of Preparation 31 (322 mg, 0.72 mmol) in dichloromethane (6 ml) was added pyridine (0.4 ml) and 2,2,2-trifluoroethanesulphonyl chloride (0.2 ml, 1.80 mmol). The mixture was stirred at room temperature for 1.5 h and methanesulphonyl chloride (0.4 ml, 5.16 mmol) was added. The reaction mixture was then stirred at room temperature for 16 h. The reaction mixture was poured into ice/water (30 ml) and the mixture adjusted to pH 1 by addition of hydrochloric acid (2N). The mixture was extracted with ethyl acetate (3 x 20 ml) and the

combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (silica) with gradient elution, ethyl acetate : hexane [1 : 4 to 1 : 1]. The appropriate fractions were combined and concentrated to give Preparation 35 (200 mg).

^{1}H-NMR δ (CDCl3): 2.81 - 2.84 (3.0H), 3.01 - 3.04 (3.0H), 3.44 - 3.48 (3.0H), 4.23 - 4.30 (1.0H), 4.40 - 4.47 (1.0H), 7.82 - 7.84 (2.0H), 7.87 - 7.89 (1.0H).

Preparation 36

N-(3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-*N*-(2,2,2-trifluoroethyl)methanesulfonamide

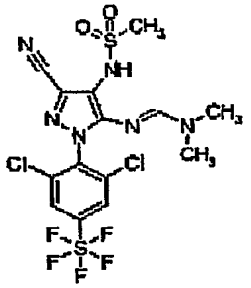


To a solution of Preparation 37 (239 mg, 0.45 mmol) in 1-methyl-2-pyrrolidinone (4 ml) was added sodium hydride (60% in oil, 12 mg, 0.50 mmol). The mixture was stirred at room temperature for 5 min and 2,2,2-trifluoroethyltrichloromethane sulphonate (166 mg, 0.59 mmol) was added. The reaction mixture was then stirred for 18 h at room temperature. To the reaction mixture was added brine (10 ml) and the mixture was adjusted to pH 4 by addition of hydrochloric acid (2N). The mixture was extracted with ethyl acetate (2 x 10 ml) and the combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (silica) eluting with ethyl acetate/hexane [1 : 3]. The appropriate fractions were combined and concentrated to give Preparation 36 (82 mg).

MS (ES): M/Z [MH+] 609.0; expected mass for C16H14Cl2F8N6O2S2 + H is 609.0

Preparation 37

N-(3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)methanesulfonamide



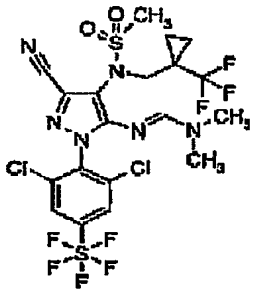
To a solution of Preparation 31 (520 mg, 1.16 mmol) in dichloromethane (10 ml) and pyridine (0.47 ml, 5.8 mmol), under nitrogen, was added 4-dimethylaminopyridine (catalytic amount) and methanesulphonyl chloride (0.22 ml, 2.90 mmol). The reaction mixture was then stirred at room temperature for 18 h. The reaction mixture was poured into water (20 ml) and hydrochloric acid (2N, 5 ml). The mixture was washed with dichloromethane (25 ml) and the two layers were separated. The aqueous phase was adjusted to pH 2 by addition of hydrochloric acid and extracted with dichloromethane (2 x 20 ml). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography with gradient elution, ethyl acetate : hexane [1 : 1 to 1 : 0]. The appropriate fractions were combined and concentrated to give Preparation 37 (508 mg).

MS (ES): M/Z [MH+] 527.0; expected mass for C14H13Cl2F5N6O2S2 + H is 527.0

^{1}H-NMR δ (CDCl3): 2.74 - 2.78 (3.0H), 3.01 - 3.04 (3.0H), 3.20 - 3.24 (3.0H), 5.91 - 5.99 (1.0H), 7.80 - 7.82 (2.0H), 8.54 - 8.57 (1.0H).

Preparation 38

N-(3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-*N*-{[1-(trifluoromethyl)cyclopropyl]methyl}methanesulfonamide

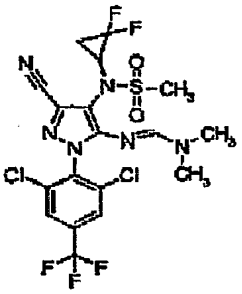


To a solution of Preparation 37 (147 mg, 0.28 mmol) in acetonitrile (6 ml) was added Preparation 60 (107 mg, 0.36 mmol) in acetonitrile (2 ml), followed by caesium carbonate (91 mg, 0.59 mmol) and potassium iodide (catalytic amount). The reaction mixture was then heated at reflux for 5 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between water (10 ml) and ethyl acetate (15 ml). The two layers were separated and the aqueous layer was adjusted to pH 1 by addition of hydrochloric acid (2N) and re-extracted with ethyl acetate (10 ml). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (silica) with gradient elution, ethyl acetate : hexane [1 : 4 to 1 : 2]. The appropriate fractions were combined and concentrated to give Preparation 38 (155 mg).

MS (ES): M/Z [MH+] 649.0; expected mass for C19H18Cl2F8N6O2S2 + H is 649.0

Preparation 39

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-*N*-(2,2-difluorocyclopropyl)methanesulfonamide



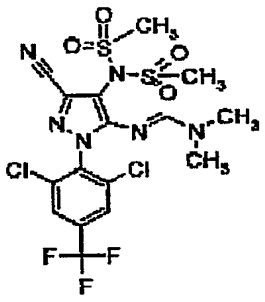
To a solution of Preparation 64 (160 mg, 0.32 mmol) in toluene (1.5 ml) was added methyl benzoate (44 mg, 0.32 mmol) in toluene and sodium fluoride (1.4 mg). This mixture was heated to 100°C and trimethylsilyl-2,2-difluoro-2-

(fluorosulphonyl)acetate (0.64 ml, 0.32 mmol) was added dropwise via syringe, over 2 hours. The reaction mixture was concentrated *in vacuo* and the residue was pre-absorbed on to silica. The silica/crude product mixture was purified by column chromatography (silica) with gradient elution, hexane : ethyl acetate [3 : 1 to 1 : 1]. The appropriate fractions were combined and concentrated to give Preparation 39 (19 mg).

MS (ES): M/Z [MH+] 544.9; expected mass for C18H15Cl2F5N6O2S + H is 545.0

Preparation 40

N-{5-amino-3-cyano-1-[2,6-dichloro-4-trifluoromethylphenyl]-5-[[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl}-*N*-(methylsulfonyl)methanesulfonamide



To a solution of Preparation 50 (220 mg, 0.56 mmol) in pyridine (5 ml), at 0°C, was added dropwise methanesulphonyl chloride (130 mg, 0.09 ml, 1.13 mmol). The reaction mixture was then allowed to warm to room temperature for 18 h. The reaction mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane (20 ml) and hydrochloric acid (1N, 20 ml). The organic phase was separated, washed with brine (20 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography with gradient elution, ethyl acetate : hexane [1 : 2 to 1 : 1 to 1 : 0]. The appropriate fractions were combined and concentrated to give Preparation 40 (200 mg), which was slightly contaminated with *mono*-sulfonamide, ratio of *bis*-sulfonamide : *mono*-sulfonamide (4 : 1).

MS (ES): M/Z [MH+] 547.4; expected mass for C16H15Cl2F3N6O4S2 + H is 547.0

^{1}H-NMR δ (CDCl3): 2.80 - 2.83 (3.0H), 3.03 - 3.05 (3.0H), 3.40 - 3.44 (6.0H), 7.70 - 7.71 (2.0H), 8.05 - 8.07 (1.0H).

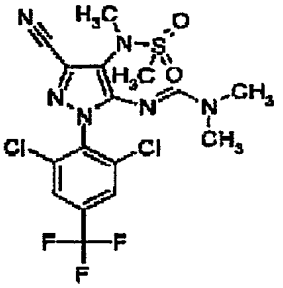
Alternative preparation

To a solution of Preparation 50 (2.3 g, 5.88 mmol) in dichloromethane (55 ml), at 0°C, was added dropwise triethylamine (2.13 ml, 15.29 mmol) and methanesulphonyl chloride (1.14 ml, 14.7 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 2 h. To the reaction mixture was added dichloromethane (50 ml) and the solution was washed with hydrochloric acid (1N, 50 ml), followed by water (100 ml) and brine (100 ml). The organic phase was separated, dried ($MgSO_4$) and concentrated *in vacuo* to give Preparation 40 (3.4 g).

MS (ES): M/Z [MH+] 547.4; expected mass for C16H15Cl2F3N6O4S2 + H is 547.0

Preparation 41

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-*N*-methylmethanesulfonamide



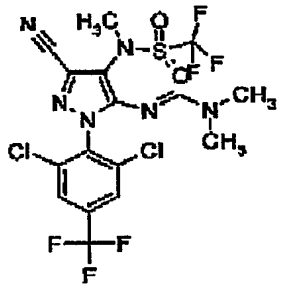
To a solution of Preparation 19 (364 mg, 0.78 mmol) in *N,N*-dimethylformamide (6 ml), at 0°C, was added potassium *tert*-butoxide (96 mg, 0.83 mmol), in *N,N*-dimethylformamide, and methyl iodide (53 µl, 0.83 mmol). The reaction mixture was warmed to room temperature over 10 min and then heated at 70°C for 1 h. After cooling to room temperature, methyl iodide (48 µl, 0.78 mmol) was added to the reaction mixture, which was stirred for 18 h at room temperature. To the reaction mixture was added ethyl acetate (30 ml) and water (30 ml) and the aqueous phase was separated and extracted with ethyl acetate. The combined organic phases were then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (silica, 20 g) with gradient elution,

cyclohexane : dichloromethane [1 : 1 to 0 : 1]. The appropriate fractions were combined and concentrated to give Preparation 41 (377 mg).

^{1}H-NMR δ (CDCl3): 2.75 - 2.78 (3.0H), 3.02 - 3.05 (3.0H), 3.18 - 3.21 (3.0H), 3.30 - 3.33 (3.0H), 7.68 - 7.71 (2.0H), 8.49 - 8.52 (1.0H).

Preparation 42

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-*N*-methyl-1,1,1-trifluoromethanesulfonamide

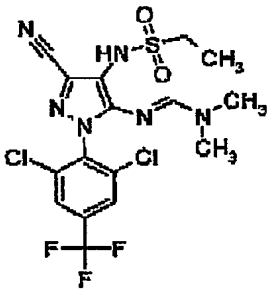


To a solution of Preparation 58 (1.3 g, 1.98 mmol) in tetrahydrofuran (11 ml), at 0°C, was added potassium carbonate (685 mg, 4.96 mmol) in methanol (11 ml) and water (3 drops). The reaction mixture was then stirred at room temperature for 2 h. The reaction mixture was concentrated *in vacuo* and to the residue was added dichloromethane. The solution was washed with hydrochloric acid (1N) and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (silica, 50 g) with gradient elution, cyclohexane : dichloromethane [1 : 0 to 0 : 1], followed by dichloromethane : methanol [95 : 5]. The appropriate fractions were combined and concentrated to give Preparation 42 (240 mg).

^{1}H-NMR δ (CDCl3): 2.79 - 2.85 (3.0H), 3.02 - 3.08 (3.0H), 3.45 - 3.51 (3.0H), 7.69 - 7.74 (2.0H), 8.02 - 8.07 (1.0H).

Preparation 43

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)ethanesulfonamide

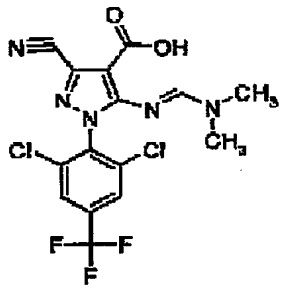


To a solution of Preparation 50 (200 mg, 0.51 mmol) in dichloromethane (4 ml) was added 4-dimethylaminopyridine (20 mg), pyridine (0.2 ml) and ethanesulphonyl chloride (72 µl, 0.76 mmol). The reaction mixture was then stirred at room temperature for 18 h. The reaction mixture was concentrated under a stream of nitrogen to give Preparation 43 (200 mg).

MS (ES): M/Z [MH+] 483.3; expected mass for C16H15Cl2F3N6O2S + H is 483.0

Preparation 44

3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazole-4-carboxylic acid



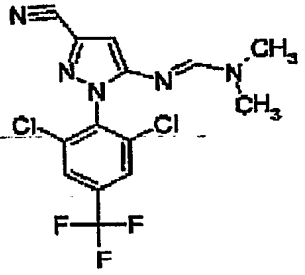
To a solution of Preparation 48 (2.0 g, 4.61 mmol) in pyridine (20 ml) was added lithium iodide (3.1 g, 23.0 mmol). The reaction mixture was heated at reflux, under nitrogen, for 20 h and then stirred at room temperature for 50 h. The reaction mixture was partitioned between hydrochloric acid (4M, 200 ml) and ethyl acetate (150 ml). The aqueous layer was separated and extracted with ethyl acetate (2 x 100 ml). The combined organic phases were then washed with hydrochloric acid (2N, 2 x 100 ml) and brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with ethyl acetate/heptane [8 : 1]. The appropriate fractions were combined and concentrated to give Preparation 44 (1.5 g) as an off-white solid.

MS (ES): M/Z [MH+] 420.2; expected mass for C15H10Cl2F3N5O2 + H is 420.0

^{1}H-NMR δ (DMSOd_6): 2.67 - 2.74 (3.0H), 3.00 - 3.07 (3.0H), 8.20 - 8.25 (2.0H), 8.41 - 8.46 (1.0H).

Preparation 45

N-{3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-5-yl}-*N*,*N*-dimethylimidoformamide

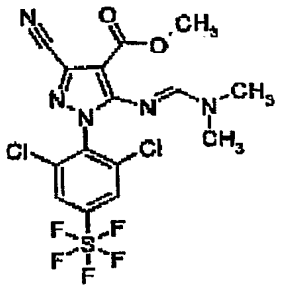


A solution of Preparation 49 (15.0 g, 47.0 mmol) in *N*,*N*-dimethylformamide dimethyl acetal (60 ml) was heated at reflux for 4 h. The reaction mixture was then stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was triturated with diethyl ether/pentane. The solution was filtered and concentrated *in vacuo* to give Preparation 45 (16.06 g).

^{1}H-NMR δ (DMSOd_6): 2.63 - 2.65 (3.0H), 2.96 - 2.98 (3.0H), 6.61 - 6.63 (1.0H), 8.13 - 8.15 (1.0H), 8.16 - 8.18 (2.0H).

Preparation 46

Methyl-3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazole-4-carboxylate



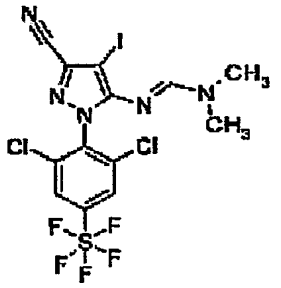
A mixture of Preparation 47 (50.0 g, 89.3 mmol), triethylamine (24.9 ml, 178.6 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II)-.dichloromethane (2.0 g) in methanol (500 ml) was heated at 65°C under carbon

monoxide (150 psi) for 8 h. To the reaction mixture was added water (2 l) and the mixture was stirred for 30 min. The precipitate was collected by filtration and air-dried to give Preparation 46 (43.3 g).

^{1}H-NMR δ (DMSOd_6): 2.67 - 2.70 (3.0H), 3.00 - 3.03 (3.0H), 3.72 - 3.77 (3.0H), 8.36 - 8.38 (1.0H), 8.41 - 8.43 (2.0H).

Preparation 47

N'-{3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-4-iodo-1*H*-pyrazol-5-yl}-*N*,*N*-dimethylimidoformamide

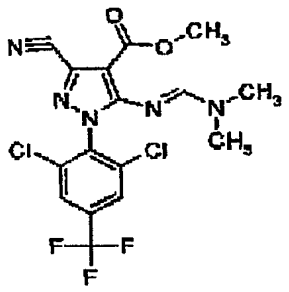


A solution of Preparation 54 (52 g, 103 mmol) in *N*,*N*-dimethylformamide dimethyl acetal (300 ml) was heated at reflux for 5 h, cooled to room temperature and stirred for 18 h. The reaction mixture was purified by column chromatography (silica, 1 kg) with gradient elution, hexane : ethyl acetate [6 : 1 to 4 : 1]. The appropriate fractions were combined and concentrated to give Preparation 47 (45 g) as a light brown solid.

^{1}H-NMR δ (CDCl3): 2.77 - 2.81 (3.0H), 3.02 - 3.05 (3.0H), 7.78 - 7.81 (2.0H), 8.21 - 8.24 (1.0H).

Preparation 48

Methyl-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-[[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazole-4-carboxylate



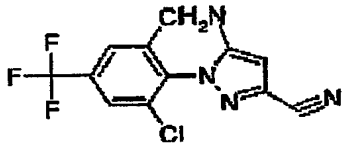
A solution of Preparation 56 (8.0 g, 21.0 mmol) in *N,N*-dimethylformamide dimethylacetal (40 ml, 0.3 mol) was heated at reflux for 2 h. The reaction mixture was concentrated *in vacuo* and the residue was recrystallised from methanol to give Preparation 48 (7.4 g) as a pale brown crystalline solid.

MS (ES): M/Z [MH+] 434.2; expected mass for C16H12Cl2F3N5O2 + H is 434.0

^{1}H-NMR δ (CDCl3): 2.76 - 2.82 (3.0H), 3.07 - 3.13 (3.0H), 3.87 - 3.93 (3.0H), [7.68 - 7.73 (2.0H), 8.59 - 8.64 (1.0H).

Preparation 49

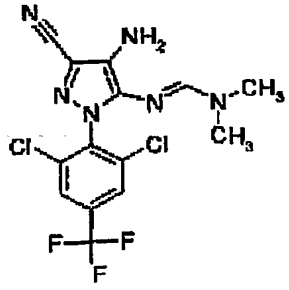
5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazole-3-carbonitrile



WO 20000462210 A2, WO 9839302 A1, US 5232940 A, EP 352944 A1

Preparation 50

N-{4-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazol-5-yl}-*N,N*-dimethylimidoformamide



To a solution of Preparation 66 (423 mg, 0.79 mmol) in tetrahydrofuran (15 ml) was added tetrabutylammonium fluoride (1M in tetrahydrofuran, 3.2 ml, 3.2 mmol). The reaction mixture was then heated at 50°C for 1 h. The reaction mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane (20 ml) and water (20 ml). The organic phase was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography with gradient elution, ethyl acetate : hexane [1 : 2 to 4 : 1]. The appropriate fractions were combined and concentrated to give Preparation 50 (220 mg, 71%).

MS (ES): M/Z [MH+] 391.2; expected mass for C14H11Cl2F3N6 + H is 391.1

^{1}H-NMR δ = (CDCl3): 2.74 - 2.83 (3.0H), 2.91 - 3.08 (5.0H), 7.65 - 7.70 (2.0H) 8.15 - 8.20 (1.0H).

Alternative synthesis

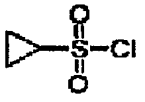
A solution of Preparation 67 (1.20 g, 2.85 mmol) in methanol (25 ml) was placed under a hydrogen atmosphere (15 psi), with platinum (5% on charcoal), at room temperature for 3 h. The reaction mixture was filtered through a pad of Arbocel®, washing through with dichloromethane/methanol and the filtrate was concentrated *in vacuo*. The residue was purified using an Isolute™ cartridge (silica, 25 g), eluting with dichloromethane/methanol [99 : 1]. The appropriate fractions were combined and concentrated to give Preparation 50 (1.0 g).

MS (ES): M/Z [MH+] 391.1; expected mass for C14H22Cl2F3N6 + H is 391.1

^{1}H-NMR δ (CDCl3): 2.73 - 2.77 (3.0H), 2.94 - 3.00 (3.0H), 7.61 - 7.73 (2.0H), 8.13 - 8.18 (1.0H).

Preparation 51

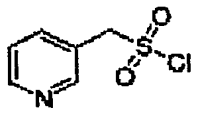
cyclopropanesulfonyl chloride



J Organic Chem, 1993, 58, 5, 1128; J Amer. Chem., 114, 9, 3492.

Preparation 52

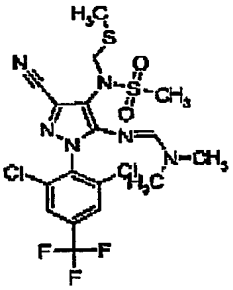
pyridin-3-ylmethanesulfonyl chloride



GB 2271111 A1, WO 9407869 A1

Preparation 53

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-*N*-[(methylthio)methyl]methanesulfonamide

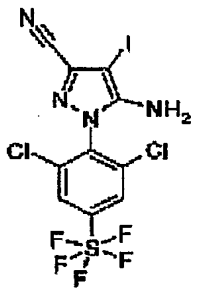


To a solution of the Preparation 19 (200 mg, 0.43 mmol) in acetone (7 ml) was added potassium carbonate (88 mg, 0.64 mmol), followed by chloro(methylthio)methane (53.2 µl, 0.64 mmol). The reaction mixture was then heated at reflux for 2 h. The reaction mixture was concentrated under nitrogen and the residue partitioned between ethyl acetate and water. The two layers were separated and the aqueous layer was extracted with ethyl acetate (x 2). The combined organic phases were dried ($MgSO_4$) and concentrated under nitrogen to give Preparation 53 (275 mg).

MS (ES): M/Z [MH+] 531.0; expected mass for C17H17Cl2F3N6O2S2 + H is 529.0

Preparation 54

5-amino-1-[2,6-dichloro-4-pentafluorothiophenyl]-4-iodo-1*H*-pyrazole-3-carbonitrile

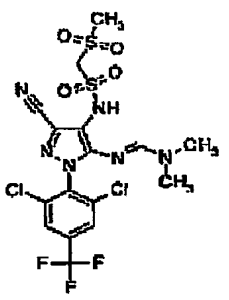


To a solution of Preparation 57 (40.0 g, 106 mmol) in acetonitrile (400 ml) was added *N*-iodosuccinimide (26.4 g, 117 mmol) and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with ethyl acetate (1 l) and washed with aqueous sodium thiosulphate solution (10%, 3 x 500 ml) and brine (500 ml). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give Preparation 54 (53 g) as a brown solid.

^{1}H-NMR δ (CDCl3): 3.87 - 3.94 (2.0H), 7.88 - 7.90 (2.00)H.

Preparation 55

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-1-(methylsulfonyl)methanesulfonamide

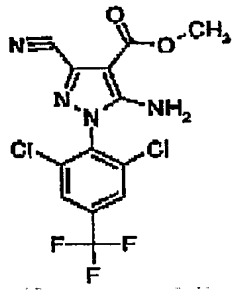


To a solution of Preparation 50 (200 mg, 0.51 mmol) in dichloromethane (4 ml) was added 4-dimethylaminopyridine (20 mg), pyridine (0.2 ml) and methylmethanedisulphonyl chloride (147 mg, 0.76 mmol). The reaction mixture was then stirred at room temperature for 18 h. The reaction mixture was concentrated under a stream of nitrogen to give Preparation 55 (100 mg).

MS (ES): M/Z [MH+] 547.0; expected mass for C16H15Cl2F3N6O4S2 + H is 547.0

Preparation 56

Methyl-5-amino-3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1*H*-pyrazole-4-carboxylate

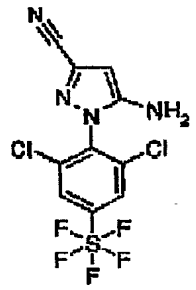


A mixture of Preparation 65 (18 g, 40.3 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (600 mg) and triethylamine (10 ml), in methanol (150 ml), was placed in a pressure vessel and heated at 60°C under carbon monoxide (100 psi) for 60 h. The reaction mixture was filtered through Celite® and the filtrate concentrated *in vacuo*. To the residue was added ethyl acetate and this solution was washed with hydrochloric acid (0.2M) and brine. The organic phase was then separated, dried and concentrated *in vacuo*. Purification: The residue was purified by flash column chromatography, eluting with ethyl acetate/hexane (1 : 5). The appropriate fractions were combined and concentrated and the residue re-crystallised from methanol to give Preparation 56 (100 mg) as a crystalline solid.

MS (ES): M/Z [MH+] 379.0; expected mass for C13H7Cl2F3N4O2 + H is 379.0

Preparation 57

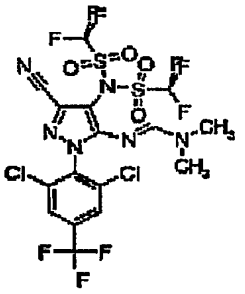
5-amino-1-[2,6-dichloro-4-pentafluorothiophenyl]-1*H*-pyrazole-3-carbonitrile



WO 9306089 A1, EP 605469 A1

Preparation 58

N-{5-amino-3-cyano-1-[2,6-dichloro-4-trifluoromethylphenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl}-*N*-(trifluoromethylsulfonyl)trifluoromethanesulfonamide

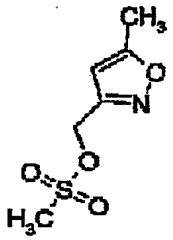


To a solution of Preparation 50 (800 mg, 2.05 mmol) in anhydrous dichloromethane (20 ml), at 0°C, was added triethylamine (716 µl, 4.10 mmol) and trifluoromethanesulphonic anhydride (860 µl, 2.05 mol). The reaction mixture was then stirred under nitrogen for 30 min. To the reaction mixture was added dichloromethane and hydrochloric acid (2M, 40 ml). The organic phase was separated, washed with hydrochloric acid (2M) and brine, dried (Na_2SO_4) and concentrated *in vacuo* to give Preparation 58 (1.3 g).

MS (ES): M/Z [MH+] 655.3; expected mass for C16H9Cl2F9N6O4S2 + H is 654.9

Preparation 59

(5-methylisoxazol-3-yl)methyl methanesulfonate

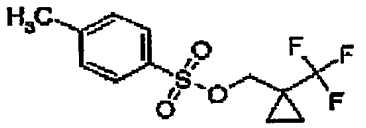


To a solution of 3-hydroxymethyl-5-methylisoxazole (100 mg, 0.88 mmol) in dry pyridine (2 ml), at 0°C, was added methanesulphonyl chloride (103 µl, 1.32 mmol). The reaction mixture was then stirred at room temperature for 3 h.

Workup: The reaction mixture was poured into an ice/water mixture and extracted with diethyl ether (x 3). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give Preparation 59, which was used directly.

Preparation 60

[1-(trifluoromethyl)cyclopropyl]methyl 4-methylbenzenesulfonate

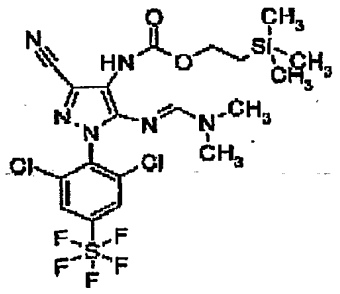


To a solution of Preparation 69 (8.18 g, 58.4 mmol) in dichloromethane (50 ml), at 0°C, was added triethylamine (50 ml), 4-dimethylaminopyridine (713 mg, 5.84 mmol) and *p*-toluenesulphonyl chloride (11.1 g, 58.4 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between diethyl ether (250ml) and hydrochloric acid (0.5M, 100 ml). The two layers were separated and the aqueous phase was extracted with diethyl ether (100 ml). The combined organic phases were washed with saturated aqueous sodium hydrogen carbonate solution (50 ml) and brine (50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified using a Biotage™ Flash 40 system with gradient elution, diethyl ether : cyclohexane [5 : 95 to 20 : 80]. The appropriate fractions were combined and concentrated to give Preparation 60 (11.8 g).

^{1}H-NMR δ (CDCl3): 0.81 - 0.89 (2.0H), 1.09 - 1.16 (2.0H), 2.44 - 2.48 (3.0H), 4.09 - 4.12 (2.0H), 7.33 - 7.39 (2.0H), 7.77 - 7.82 (2.0H).

Preparation 61

2-(trimethylsilyl)ethyl 3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-ylcarbamate

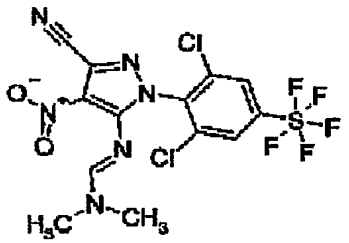


To a solution of Preparation 18 (6.7 g, 14.0 mmol), triethylamine (2.14 ml, 15.4 mmol) and 2-trimethylsilylethanol (2.21 ml, 15.4 mmol) in 1,4-dioxane (100 ml) was added diphenylphosphoryl azide (3.34 ml, 15.4 mmol). The reaction mixture was heated at reflux for 3 h and then stirred for 18 h at room temperature. To the reaction mixture was added ethyl acetate (200 ml) and the mixture was washed with hydrochloric acid (1M, 2 x 250 ml). The aqueous phase was re-extracted with ethyl acetate (200 ml) and the organic phases were combined, washed with brine (200 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (silica, 300 g) with gradient elution, methanol : dichloromethane [0 : 100 to 5 : 95]. The appropriate fractions were combined and concentrated to give Preparation 61 (9.0 g).

MS (ES): M/Z [MH+] 593.0; expected mass for C19H23Cl2F5N6O2SSi + H is 593.1

Preparation 62

N'-{3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-4-nitro-1*H*-pyrazol-5-yl}-*N*,*N*-dimethylimidoformamide



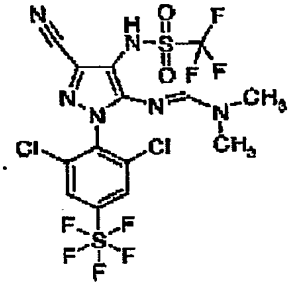
To a solution of nitronium tetrafluoroborate (470 mg, 3.5 mmol) in acetonitrile (15 ml) was added Preparation 10 (1.0 g, 2.9 mmol). The reaction mixture was then stirred at room temperature for 2 h. The reaction mixture was diluted with ethyl acetate, washed with water and saturated brine solution, dried ($MgSO_4$) and concentrated *in vacuo* to give Preparation 62 (960 mg).

MS (ES): M/Z [MH+] 478.8; expected mass for C13H9Cl2F5N6O2S + H is 479.0

^{1}H-NMR δ (CDCl3): 2.83 - 2.88 (3.0H), 3.13 - 3.16 (3.0H), 7.81 - 7.86 (2.0H), 8.44 - 8.48 (1.0H).

Preparation 63

N-(3-cyano-1-[2,6-dichloro-4-pentafluorothiophenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-1,1,1-trifluoromethanesulfonamide

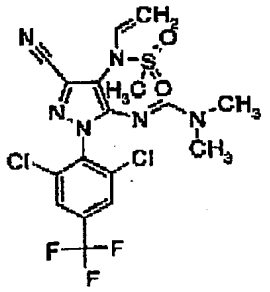


To a solution of Preparation 31 (200 mg, 0.45 mmol) in anhydrous dichloromethane (5 ml), at 0°C, was added triethylamine (124 µl, 0.89 mmol) and trifluoromethanesulphonic anhydride (150 µl, 0.89 mol). The reaction mixture was then stirred under nitrogen for 30 min. To the reaction mixture was added dichloromethane and hydrochloric acid (4M, 3 ml). The organic phase was separated, washed with hydrochloric acid (4M) and brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (silica, 25 g) with gradient elution, ethyl acetate : cyclohexane [2 : 1 to 1 : 0], followed by methanol. The appropriate fractions were combined and concentrated to give Preparation 63 (200 mg).

MS (ES): M/Z [MH+] 580.9; expected mass for C14H10Cl2F8N6O2S2 + H is 581.0

Preparation 64

N-(3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-yl)-*N*-vinylmethanesulfonamide

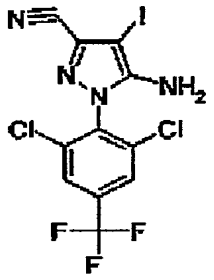


To a solution of Preparation 33 (414 mg, 0.72 mmol) in dimethyl sulphoxide (5 ml) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.13 ml, 0.86 mmol). The reaction mixture was stirred for 18 h, and further 1,8-diazabicyclo[5.4.0]undec-7-ene (0.13 ml, 0.86 mmol) was added. The reaction mixture was then stirred for another 18 h. To the reaction mixture was added saturated aqueous sodium chloride solution (20 ml) and ethyl acetate. The two layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 10 ml). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (silica) with gradient elution, hexane : ethyl acetate [4 : 1 to 2 : 1]. The appropriate fractions were combined and concentrated to give Preparation 64 (230 mg).

MS (ES): M/Z [MH+] 495.0; expected mass for C17H15Cl2F3N6O2S + H is 495.0

Preparation 65

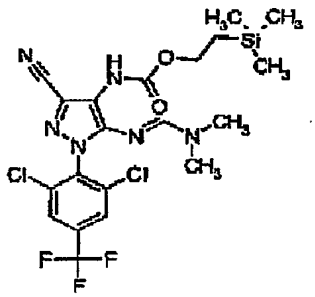
5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-iodo-1*H*-pyrazole-3-carbonitrile



US 6069157 A, EP 933363 A1, WO 9828278 A1

Preparation 66

2-(trimethylsilyl)ethyl 3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-5-{[(1*E*)-(dimethylamino)methylene]amino}-1*H*-pyrazol-4-ylcarbamate



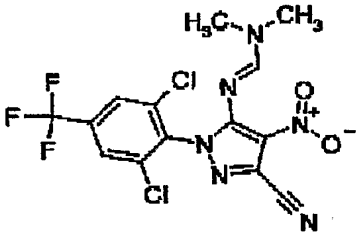
To a solution of Preparation 44 (420 mg, 1.0 mmol) in 1,4-dioxane (6 ml) was added triethylamine (0.15 ml, 1.1 mmol) and 2-(trimethylsilyl)ethanol (0.16 ml, 1.1 mmol), followed by the dropwise addition of diphenylphosphoryl azide (0.24 ml, 1.1 mmol). The reaction mixture was then heated at reflux for 18 h. The reaction mixture was concentrated *in vacuo* and the residue partitioned between ethyl acetate (20 ml) and hydrochloric acid (1N, 20 ml). The organic phase was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography with gradient elution, ethyl acetate : hexane [1 : 2 to 2 : 1]. The appropriate fractions were combined and concentrated to give Preparation 66 (423 mg, 80%).

MS (ES): M/Z [MH+] 535.4; expected mass for C20H23Cl2F3N6O2Si + H is 535.1

^{1}H-NMR δ (CDCl3): -0.22 - 0.21 (9.0H), 0.95 - 1.07 (2.0H), 2.67 - 2.78 (3.0H), 2.88 - 2.99 (3.0H), 4.17 - 4.30 (2.0H), 7.03 - 7.12 (1.0H), 7.59 - 7.71 (2.0H), [7.88 - 7.99 (1.0H).

Preparation 67

N-{3-cyano-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-nitro-1*H*-pyrazol-5-yl}-*N*,*N*-dimethylimidoformamide

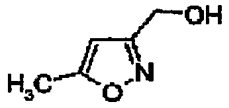


To a solution of nitronium tetrafluoroborate (9.30 g, 70.0 mmol) in acetonitrile (200 ml) was added Preparation 45 (18.82 g, 50.0 mmol) over 5 min. The reaction mixture was then stirred at room temperature for 2 h. The reaction mixture was concentrated *in vacuo* and to the residue was added acetonitrile/ethyl acetate (1 : 9, 1000 ml). The solution was washed with water (200 ml) and saturated brine solution (300 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was triturated with diethyl ether/pentane and the solution was concentrated *in vacuo* to give Preparation 67 (15.6 g).

^{1}H-NMR δ (DMSOd_6): 2.73 - 2.77 (3.0H), 3.06 - 3.09 (3.0H), 8.20 - 8.27 (2.0H), 8.53 - 8.56 (1.0H).

Preparation 68

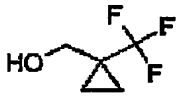
(5-methylisoxazol-3-yl)methanol



US 4451476; Can J Chem, 1990, 68, 8, 1271; Drug Design and Discovery, 1992, 8, 3, 165.

Preparation 69

[1-(trifluoromethyl)cyclopropyl]methanol



J. Fluorine Chem., 2001, 109, 2, 95

GENERIC PROCEDURES

Method 1 (Reaction)

To a solution of the protected amine in methanol (~15ml/mmol equivalent of amine) was added hydrochloric acid (4N, ~ 5ml/mmol equivalent of amine) and the reaction mixture was heated at reflux for 4 h.

Method 1 (Workup)

To the reaction mixture was added ethyl acetate (10 ml) and water (10 ml). The two layers were separated and the aqueous layer was re-extracted with ethyl acetate (10 ml x 3). The combined organic layers were dried ($MgSO_4$) and concentrated under nitrogen.

Method 3 (Reaction)

To a solution of the sulphonamide (100 mg, 0.21 mmol) in acetone (4 ml) was added potassium carbonate (38 mg, 0.28 mmol), followed by the halide (0.26 mmol). The reaction mixture was then heated at reflux for 2 h.

Method 3 (Workup)

The reaction mixture was concentrated under nitrogen and the residue partitioned between ethyl acetate (10 ml) and water (10 ml). The two layers were separated and the aqueous layer was extracted with ethyl acetate (10 ml x 2). The combined organic phases were dried ($MgSO_4$) and concentrated under nitrogen to give the final product.